Field guide to the detection and control of xerophthalmia

A. SOMMER

World Health Organization

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 150 countries exchange their knowledge and experience with the aim of achieving the highest possible level of health throughout the world.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environment conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activites, such as developing systems of primary health care that reach the whole population of Member countries ; promoting the health of mothers and children ; combating malnutrition ; eradicating smallpox throughout the world ; controlling malaria and other communicable diseases including tuberculosis and leprosy ; promoting mass immunization campaigns against a number of preventable diseases ; improving mental health ; providing safe water supplies ; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals ; recommending international nonproprietary names for drugs ; administering the International Health Regulations ; revising the international classification of diseases and causes of death ; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

FIELD GUIDE TO THE DETECTION AND CONTROL OF XEROPHTHALMIA

ALFRED SOMMER

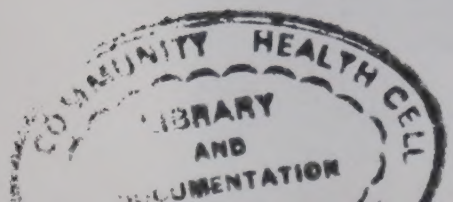
Principal Investigator
Helen Keller International
Indonesian Nutritional Blindness Prevention Project

Visiting Professor of Ophthalmology
University of Padjadjaran
Bandung, Indonesia

WORLD HEALTH ORGANIZATION
GENEVA
1978

The publication of this guide was made possible through a grant to Helen Keller International, 22 West 17th Street, New York 10011, from the United States Agency for International Development (USAID).

ISBN 92 4 154 127 X



PRINTED IN SWITZERLAND

CONTENTS

PREFACE

XEROPHTHALMIA *remains an important cause of childhood blindness in developing countries, accounting for 20 000–100 000 new cases annually. Recognizing the gravity of the situation, the Twenty-Fifth World Health Assembly in 1972 urged an intensification of activities to prevent needless loss of sight, identifying xerophthalmia as one of the three most important causes of preventable blindness in the world today. Various agencies and governments have since expressed the need for a simple, practical field guide for clinicians, nurses, and public health officials involved in the diagnosis, treatment, and prevention of this appalling disease. This manual attempts to fill that need.*

Much of the material is drawn from recent meetings and discussions which have already resulted in two useful publications: Vitamin A Deficiency and Xerophthalmia,[1] *a comprehensive discussion of the problem, and* Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia,[2] *a detailed description of assessment, prevention, and evaluation procedures.*

---

[1] WHO Technical Report Series, No. 590, 1976 (*Vitamin A deficiency and xerophthalmia.* Report of a joint WHO/USAID meeting).

[2] INTERNATIONAL VITAMIN A CONSULTATIVE GROUP (IVACG). *Guidelines for the eradication of vitamin A deficiency and xerophthalmia*, New York, The Nutrition Foundation, 1975.

INTRODUCTION

XEROPHTHALMIA has been recognized for thousands of years, and the ancient Egyptians appropriately prescribed liver as a cure. As recently as the late nineteenth and early twentieth centuries numerous cases still occurred among malnourished individuals in such widely scattered points of the globe as Brazil, China, England, Japan, and Russia.

Today the precise size and geographical distribution of the xerophthalmia problem are unknown. In recent years, the disease has been reported mainly from the rice-eating areas of South Asia, but it also occurs in Africa, Latin America, the Caribbean, and the Eastern Mediterranean.

Modern ideas about the disease date from Bloch's observations [1] that children raised in Danish orphanages on diets deficient in milk and milk products developed severe generalized malnutrition and xerophthalmia, while children raised in otherwise identical fashion, but fed dairy products, did not. He reasoned that dairy products contained a fat-soluble element essential to normal growth and ocular health and correctly equated it with vitamin A.

By the 1930s, histopathological observations by Wolbach and others [2] had demonstrated that the primary role of vitamin A was the maintenance of normal epithelial integrity. The exact mechanism involved is, however, still obscure.

---

[1] BLOCH, C. E. *J. Hyg.*, **19**: 283 (1921); *Am. J. Dis. Child.*, **27**: 139 (1924); *Am. J. Dis. Child.*, **28**: 659 (1924).

[2] WOLBACH, S. B. & HOWE, P. R. *J. exp. Med.*, **47**: 753 (1925); *Arch. Pathol. Lab. Med.*, **5**: 239 (1928).

VITAMIN A METABOLISM

VITAMIN A, or retinol, is a fat-soluble substance found in liver, particularly fish liver, and in poultry, meat, and dairy products. Carotenes—potential precursors present in green leafy vegetables, red palm oil, yellow fruits, and the like—can be converted to retinol in the wall of the gut. The relative biological values of these various substances were formerly expressed in international units (IU) of vitamin A activity,[1] 1 IU being equivalent to 0.3 μg of retinol, 0.55 μg of retinol palmitate, 0.6 μg of β-carotene, and 1.2 μg of other provitamin A carotenoids. Not only are carotenes biologically less active than retinol, but their dietary sources are less efficiently processed and absorbed from the gut. One must therefore ingest six times as much β-carotene (by weight) as retinol for a similar degree of effect.

Some 50–90 % of ingested retinol is absorbed in the small intestine and transported, in association with chylomicra, to the liver where it is stored primarily as retinol palmitate. When needed, it is released into the bloodstream in combination with retinol-binding protein (RBP), a specific carrier protein elaborated by the liver. The retinol is then removed from the serum and utilized by epithelial cells throughout the body. The diagram overleaf gives a simplified schematic outline of these metabolic pathways.

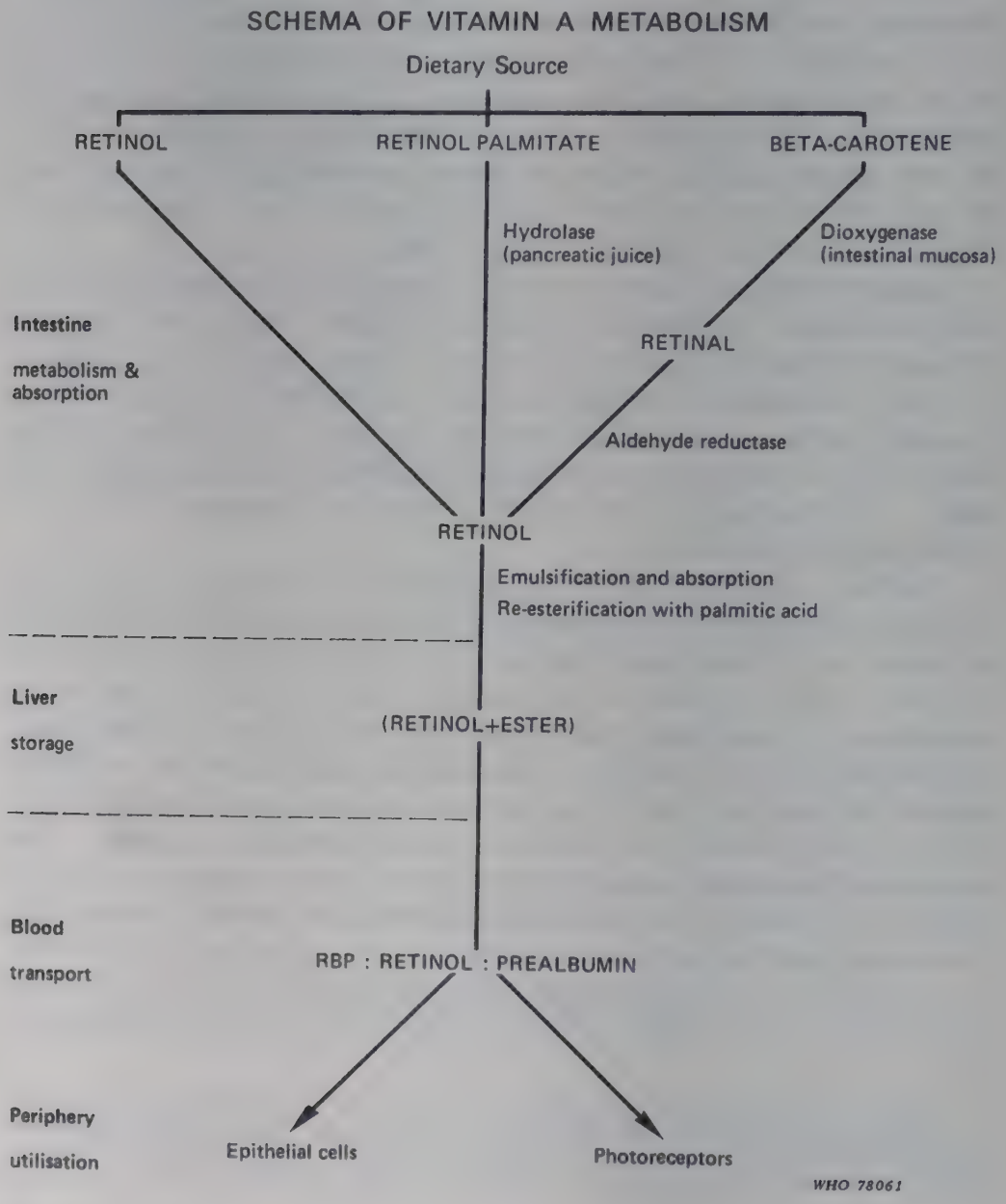
The liver stores form an important buffer for variations in vitamin A and β-carotene intake. When vitamin A intake surpasses 300–1200 μg/day of retinol, or its equivalent, the excess is stored and liver reserves are increased. When vitamin A intake is less than this amount, liver stores are drained to maintain serum retinol (vitamin A) at a normal level (above 200 μg/l or 0.7 μmol/l). When intake remains low for prolonged periods of time the liver stores become depleted, serum retinol levels drop, epithelial function is impaired, and xerophthalmia appears. The duration of inadequate intake required for this to occur depends upon the amount of vitamin A (or precursor) ingested, the extent of pre-existing liver stores, and the rate at which vitamin A is being utilized by the body.

A child with borderline, marginal intake to begin with will have very limited stores. Any sudden drop in intake, either from a change in diet

[1] The International units for vitamin A and provitamin A were discontinued in 1954 and 1956 respectively. However, since their use persists, particularly in the labelling of capsules and injectable preparations, all intakes and dosages mentioned in this book are expressed both in micrograms (μg) or milligrams (mg) and in the former international units.

or interference with absorption (as in gastroenteritis) or a sudden increase in metabolic demand (febrile state or growth spurt), will quickly deplete the limited reserves and may precipitate frank corneal destruction, even in eyes that had previously appeared entirely normal. Where liver stores have been very high, however, an individual may go for months without vitamin A and not suffer serious consequences.

The availability of stored vitamin A will also depend upon the child's general nutritional status. Severely malnourished, protein-deficient children synthesize RBP at a much reduced rate. Serum retinol levels will therefore be subnormal, even if liver stores are high. Finally, a diseased liver cannot store as much vitamin, or make as much RBP, as a normal one.



CLINICAL CLASSIFICATION AND DIAGNOSIS

VITAMIN A deficiency is a systemic disease affecting epithelial structures in a variety of organs, the eye being the most obvious and dramatic example. Keratinizing metaplasia of the respiratory and intestinal epithelia is thought to be responsible for the pulmonary and gastrointestinal symptoms found in the most severely affected children. But the classic clinical expression, present in mild to severe form, is xerophthalmia, or "dry eye".

Fig. 1 indicates the principal sites at which xerophthalmia lesions occur. With proper treatment, alterations in the retina (night blindness) and conjunctiva (xerosis and Bitot's spots) usually clear without significant sequelae. But corneal involvement (xerosis, ulcers, and keratomalacia), presented diagrammatically in Fig. 2, usually results in some degree of opacification and loss of vision, and all too often in blindness. Proper treatment, however, may still limit the extent of corneal damage, or prevent it entirely in the opposite eye if it is not yet affected.

The major xerophthalmia signs have recently been reclassified (Table 1). X1A (conjunctival xerosis) through X3B (keratomalacia) and XN (night blindness) all indicate active xerophthalmia and vitamin A deficiency requiring immediate therapy.

X1A, IB. Conjunctival xerosis and Bitot's spots

Alterations in epithelial architecture accompanying vitamin A deficiency are termed "keratinizing metaplasia". The epithelium of the

Table 1. Classification of xerophthalmia

Primary signs	
X1A	Conjunctival xerosis
X1B	Bitot's spot with conjunctival xerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
X3B	Keratomalacia
Secondary signs	
XN	Night blindness
XF	Xerophthalmia fundus
XS	Corneal scar

conjunctiva is transformed from the normal columnar to the stratified squamous type, with a resultant loss of goblet cells, formation of a granular cell layer (Fig. 3), and keratinization of the surface (Fig. 4). This is the histopathological picture of conjunctival xerosis.

Clinically, these changes are expressed as marked dryness or unwettability, the affected area appearing roughened rather than smooth and glistening. Tears, which may be plentiful, form distinct droplets, leaving the affected areas uncovered.

The entire surface of the bulbar conjunctiva may be affected. More commonly, the changes are limited to one or more patches, usually at the temporal or, less frequently, nasal limbus. The condition is almost always bilateral.

Fig. 5 and Fig. 6 depict temporal patches of conjunctival xerosis. The rest of the conjunctiva is clear and glistening, as is the cornea.

When covered by a fine foamy or cheesy material these temporal and nasal patches are known as Bitot's spots. Small to large foamy spots, some heavily pigmented, are illustrated in Fig. 7–11. The foamy material is easily wiped off, the amount present often varying from day to day. Cheese-like accretions (Fig. 12 and Fig. 13) are more tenacious, usually occurring in longer-standing disease.

Chronic vitamin A deficiency may lead to thickened plaques that persist long after the vitamin A status has returned to normal; diagnosis can only be made retrospectively, after they have failed to respond to adequate vitamin A therapy. Although they usually lack areas of true xerosis, irregular ridges and troughs may break up the light reflex and appear to be dry and non-wettable. Closer examination will usually reveal that the conjunctiva covering the narrow ridges is, in fact, "moist" and glistening.

Bitot's spots should not be confused with pinguecula or pterygium, which are more often nasal than temporal, and limited, for the most part, to adults. Pinguecula is an elevated fatty, yellowish lesion. Pterygium is fleshy and actually invades the cornea (Fig. 14).

Fig. 15 and Fig. 16 demonstrate marked, widespread conjunctival xerosis. The entire conjunctiva appears dry, roughened, and corrugated, almost skin-like. Prominent conjunctival thickening and folds are also present, but are not sufficient in themselves for diagnosis. This is an advanced lesion, frequently accompanied, as in these instances, by corneal xerosis.

X2. Corneal xerosis

Keratinizing metaplasia of the cornea is far more dangerous. Instead of being smooth, clear, and glistening, the corneal surface has a hazy, dry, roughened, often pebbly appearance, usually most marked in the

lower part. Fig. 16 and Fig. 17 illustrate early corneal haze, and Fig. 15, Fig. 18, and Fig. 19 a dry pebbly surface, demonstrated by the diffuse breakup of the light reflex. Occasionally, a tough foam-like substance may be seen tightly adhering to it (Fig. 20).

The epithelium may already be lost (erosion), but the cornea has not yet suffered permanent alteration. Prompt therapy can still restore its normal appearance.

X3A. Corneal ulceration with xerosis

Ulceration indicates destruction of the underlying stroma and results in permanent structural alteration of the cornea. When ulcers are still superficial (Fig. 21), prompt therapy may produce rapid healing with minimal residual opacification and little or no interference with vision. But deeper ulcers often perforate, resulting in iris prolapse, dense opacification (adherent leucoma), and significant reduction in visual acuity.

X3B. Keratomalacia

The most serious and least understood alteration is keratomalacia, a rapidly destructive liquefactive necrosis of the cornea, commonly resulting in perforation, extrusion of intraocular contents, and loss of the eye. Fig. 22–24 are examples of keratomalacia involving the entire cornea. In the last two, brown iris tissue is forcing its way through softened, necrotic peripheral cornea. Fig. 25 illustrates a localized area of keratomalacia, and Fig. 26, taken one month later (after treatment), shows how it has healed, leaving an adherent leucoma.

Characteristically, eyes with active corneal involvement related to vitamin A deficiency (X2, X3) are relatively "white and quiet", in sharp contrast to the red swollen lids, injected conjunctiva, and purulent discharge seen in cases of bacterial, fungal, and viral conjunctivitis and keratitis (Fig. 27). This important difference is useful in distinguishing between the two conditions. Occasionally lesions related to vitamin A deficiency become secondarily infected, in which case the accompanying malnutrition, systemic illness, and evidence of conjunctival xerosis are useful in arriving at the correct diagnosis. However, in some instances of precipitous deterioration of vitamin A status—usually brought on by measles or gastroenteritis in a child already suffering from protein-energy malnutrition—corneal involvement can precede the appearance of typical conjunctival changes.

XS. Scars

Healed sequelae of prior corneal disease related to vitamin A deficiency include opacities or scars of varying density (nebula, macula,

leucoma) as in Fig. 26, weakening and outpouching of the remaining corneal layers (staphyloma as in Fig. 28, and descemetocele as in Fig. 29) and, where loss of intraocular contents had occurred, phthisis bulbi, a scarred shrunken globe. Such end-stage lesions are not specific for xerophthalmia and may arise from numerous other conditions, notably trauma and infection.

XN. Night blindness

Retinol is essential for the elaboration of rhodopsin ("visual purple") by the rods, the sensory receptors of the retina responsible for vision under low levels of illumination. Vitamin A deficiency can interfere with rhodopsin production, impair rod function, and result in night blindness.

Night blindness of recent onset in a preschool child is practically pathognomonic of vitamin A deficiency and is frequently accompanied by conjunctival xerosis and Bitot's spots. Other causes of night blindness are relatively rare and almost never present in this fashion. Mothers are usually quick to recognize the problem, though not its cause. The children no longer move about the house or village after dusk, but prefer to sit in a secure corner, often unable to find their food or toys. In some cultures specific terms exist to describe this condition, such as "chicken eyes".

The diagnosis is usually made from the mother's history. Objective evaluation, comparing the response of the affected child with those of his normal peers after sunset or in a darkened room, is both impractical and unnecessary in most routine clinical situations.

XF. Xerophthalmia fundus

The small white retinal lesions described in some cases of vitamin A deficiency are at present of investigational interest only (Fig. 30).

All children suspected, or at risk, of having xerophthalmia must have *both* eyes examined in open shade or with the aid of a flashlight and loupe, if available. Unfortunately, because of the pain and reflex blepharospasm accompanying corneal involvement, these children tend to keep their eyes tightly shut. When necessary, the child's head can be stabilized by a parent or attendant, while a *physician* carefully separates the lids with a sterile Desmarres retractor, lid speculum, or bent paper-clip (as seen in most of the illustrations). The leading edge of the clip should be held parallel to the lid. Once it has passed behind the lid margin it should be gently angled forward, to avoid abrading the cornea or placing undue pressure on the globe.

EPIDEMIOLOGY

XEROPHTHALMIA results from an insufficient supply of vitamin A to the eye. The cause of such a deficiency can be quite complex, and depends upon the type and amount of vitamin and provitamin (primarily β-carotene) ingested, the absorptive, transport, and storage capacities of the individual, and his metabolic needs. Seemingly unrelated disease states can dramatically alter each of these parameters and, in turn, the child's vitamin A balance. For example, gastroenteritis will change the types and amounts of food offered to the child and his appetite, while the shortened transit time will decrease absorption of what vitamin A is ingested. If he is already protein-deficient, transport and storage may be decreased and the fever will increase his metabolic needs.

The cause and contribution of each of these factors will vary from one community to another, resulting in different epidemiological patterns in respect of age, sex, season, magnitude, and relative proportion of cases with and without corneal involvement.

A general pattern, however, seems to exist. Vitamin A deficiency can occur at any age, but clinical xerophthalmia is predominantly a disease of young children. The prevalence of milder manifestations (night blindness, Bitot's spots, and conjunctival xerosis) usually increases from the age of about 2 years up to the early school years. In some areas males are more commonly affected than females. Malnutrition, if present, is usually mild. These signs may persist for months, tend to be seasonal, and usually disappear spontaneously, probably with increased availability and consumption of foods containing vitamin A (and carotene). They probably represent relatively mild, isolated vitamin A deficiency and do little lasting damage, but they identify children at increased risk of developing destructive corneal lesions.

Children suffering from forms of the disease destructive to the cornea are usually younger (often less than 1 year of age), more severely malnourished, and more deficient in vitamin A. History of a recent precipitating event (pneumonia, measles, gastroenteritis, tuberculosis, etc.) is

common, and mortality is often quite high (20–50 %). The relevant patterns are summarized in Table 2.

Children born to mothers deficient in vitamin A are particularly vulnerable. Their liver stores of this vitamin are negligible, and what breast milk they receive contains little of it. All too often the quantity of breast milk itself is reduced and supplemented, or supplanted entirely, by dilute sweetened condensed milk, which is low in vitamin A.

Although severe protein-energy malnutrition is a common accompaniment of corneal involvement, the mechanism is as yet unclear. It may have a direct, deleterious action on corneal metabolism, independent of or synergistic with that of vitamin A deficiency; it may exert an indirect effect by interfering with the storage and transport of vitamin A; or it may simply reflect the general severely deficient state of the individual.

Table 2. Epidemiological distinction between conjunctival and corneal xerophthalmia

	Conjunctival (X1A, X1B)	Corneal (X2, X3)
Age (peak incidence) [a]	3–6 years	6 months–3 years
Protein-energy malnutrition	Usually mild	Usually severe
Precipitating illnesses: gastroenteritis exanthematous disease respiratory tract infection	Uncommon	Common

[a] Either form of the disease can occur at any age. Most cases, however, fall within the indicated range of peak incidence.

Colour plates

Fig. 1. Diagram indicating sites affected by xerophthalmia
Fig. 2. Diagrammatic representation of xerophthalmia lesions
Fig. 3. Conjunctival xerosis with a prominent granular cell layer and keratinized surface (haematoxylin and eosin). ×250
Fig. 4. Conjunctival xerosis specially stained to demonstrate the heavily keratinized surface (Dane's stain). ×185
Fig. 5. X1A
Fig. 6. X1A
Fig. 7–11. X1B ("foamy")
Fig. 12. X1B ("cheesy")
Fig. 13. X1B ("cheesy")
Fig. 14. Pterygium
Fig. 15. X1A (generalized), X2
Fig. 16. X1A (generalized), X2
Fig. 17. X2 (haze)
Fig. 18. X1A, X2
Fig. 19. X2
Fig. 20. X1A, X2 (with tenacious "foam")
Fig. 21. X1A, X3A
Fig. 22. X1B, X3B (generalized)
Fig. 23. X1B, X3B (generalized)
Fig. 24. X1B, X3B (generalized)
Fig. 25. X1B, X3B (localized)
Fig. 26. XS (adherent leucoma)
Fig. 27. Keratitis
Fig. 28. XS (staphyloma)
Fig. 29. XS (descemetocele)
Fig. 30. XF

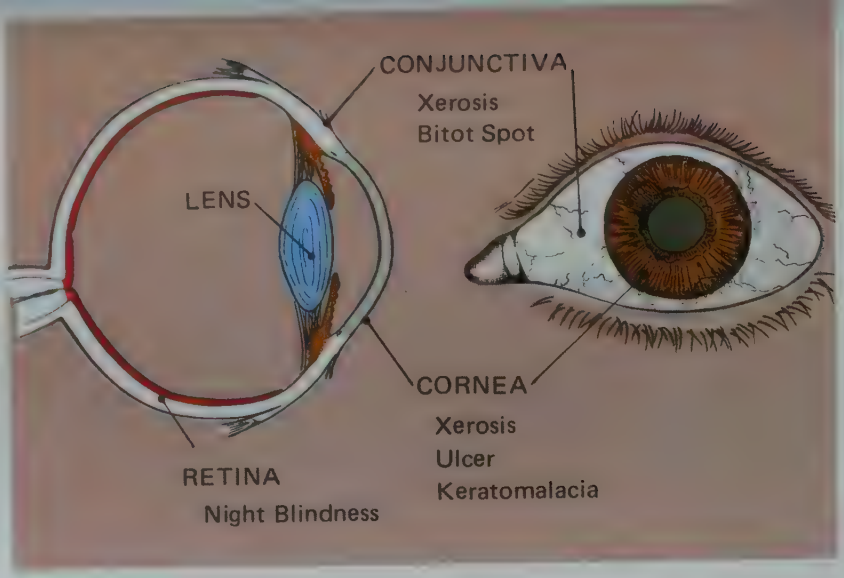


Fig. 1. Diagram indicating sites affected by xerophthalmia

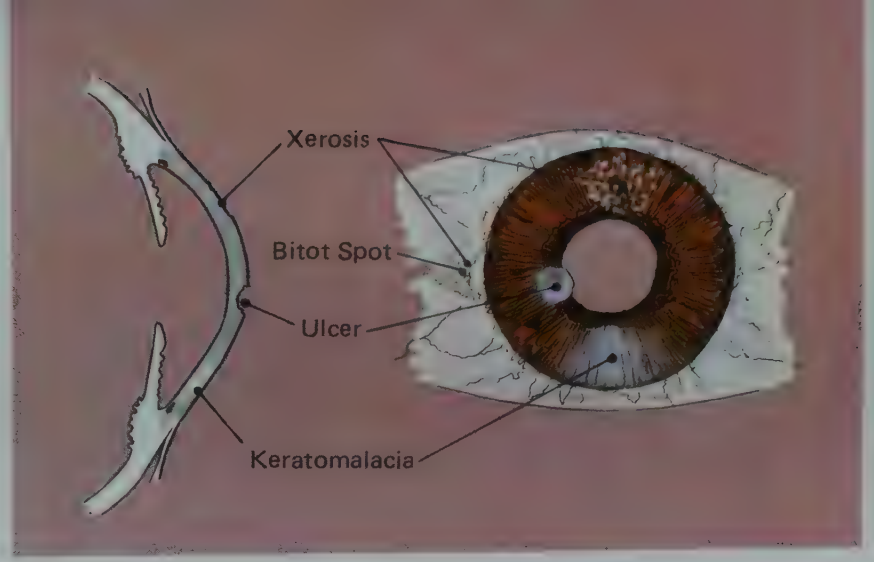


Fig. 2. Diagrammatic representation of xerophthalmia lesions

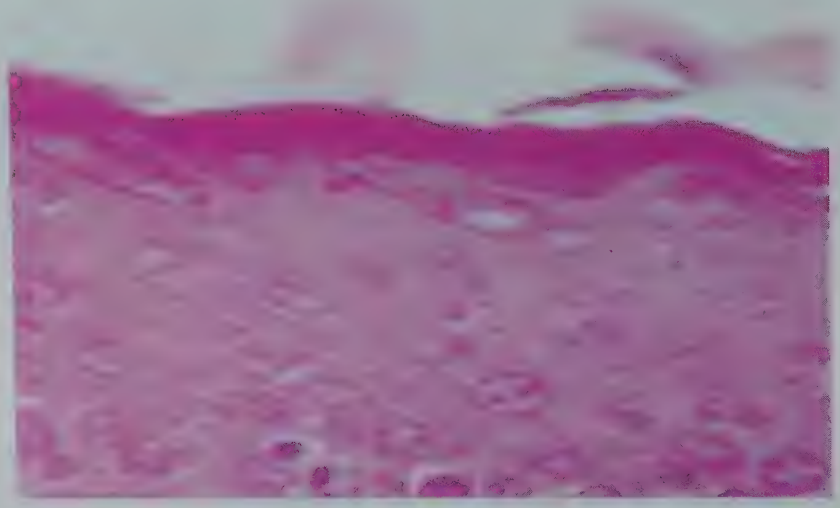


Fig. 3. Conjunctival xerosis with a prominent granular cell layer and keratinized surface (haematoxylin and eosin). ×250

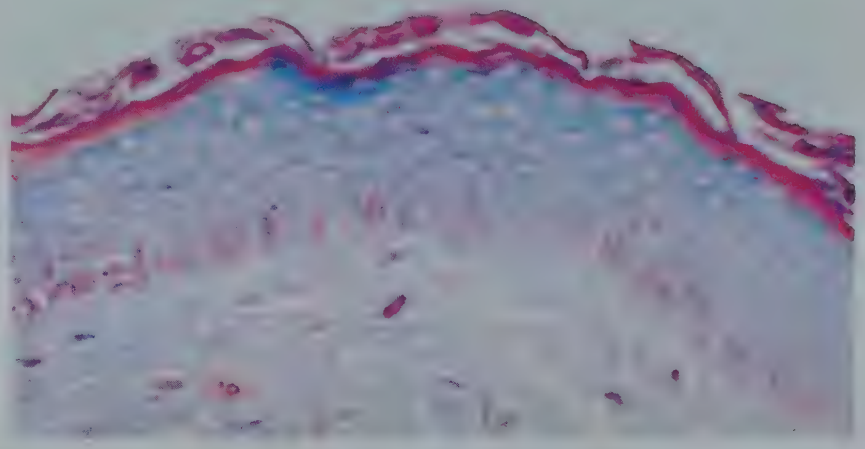


Fig. 4. Conjunctival xerosis specially stained to demonstrate the heavily keratinized surface (Dane's stain). ×185

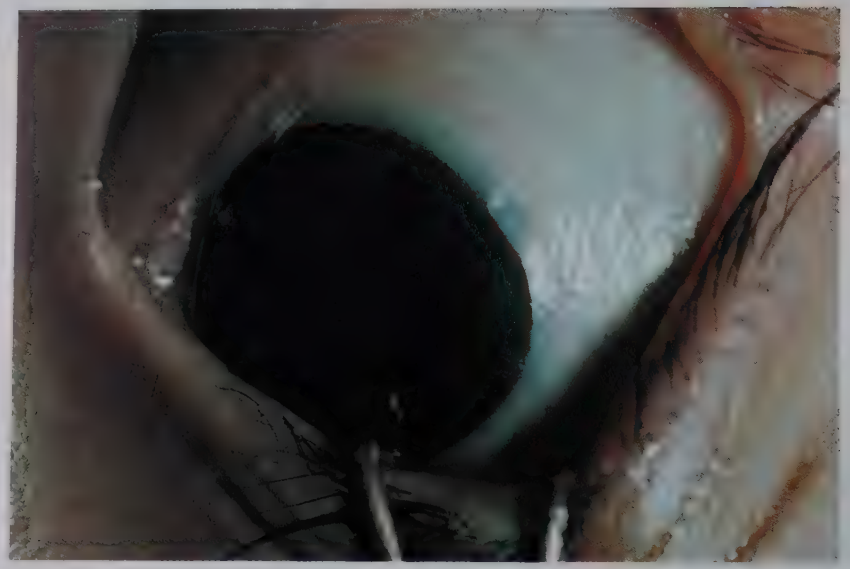
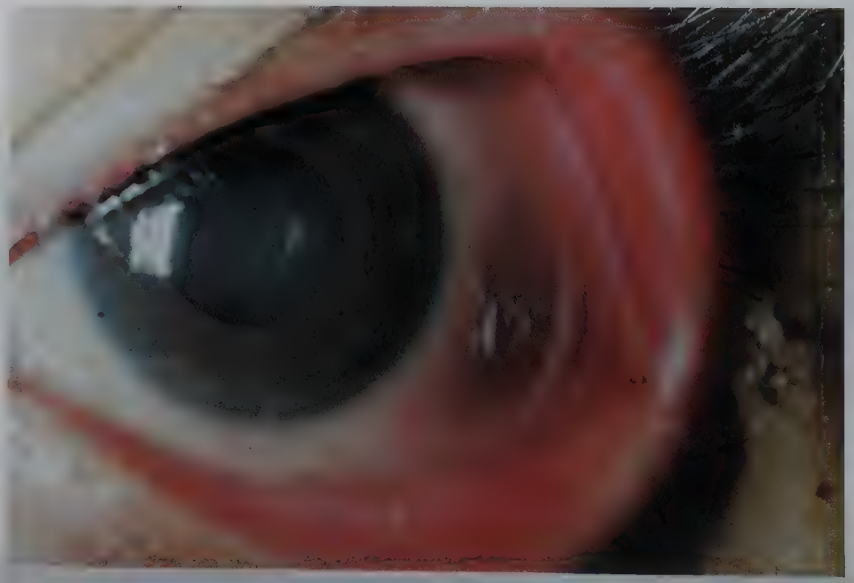


Fig. 5. X1A

Fig. 6. X1A



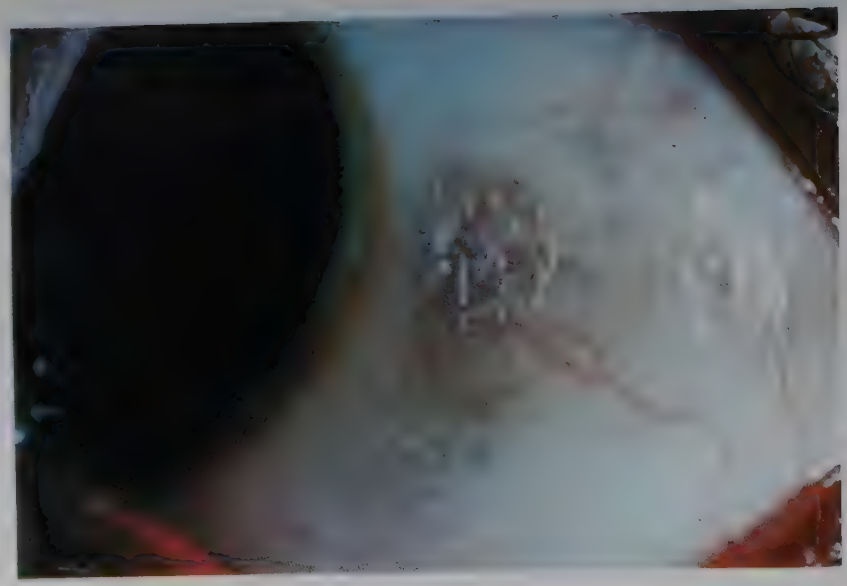


Fig. 9. X1B ("foamy")

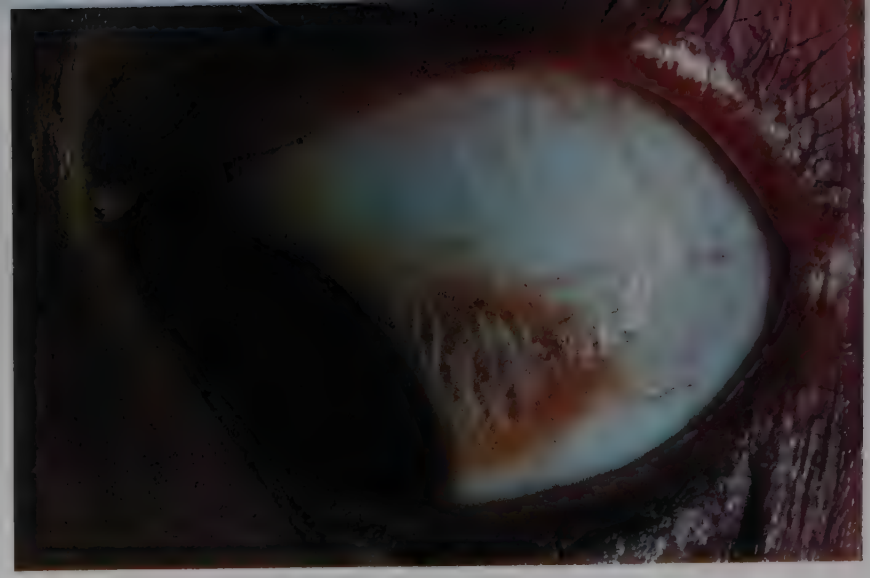


Fig. 10. X1B ("foamy")

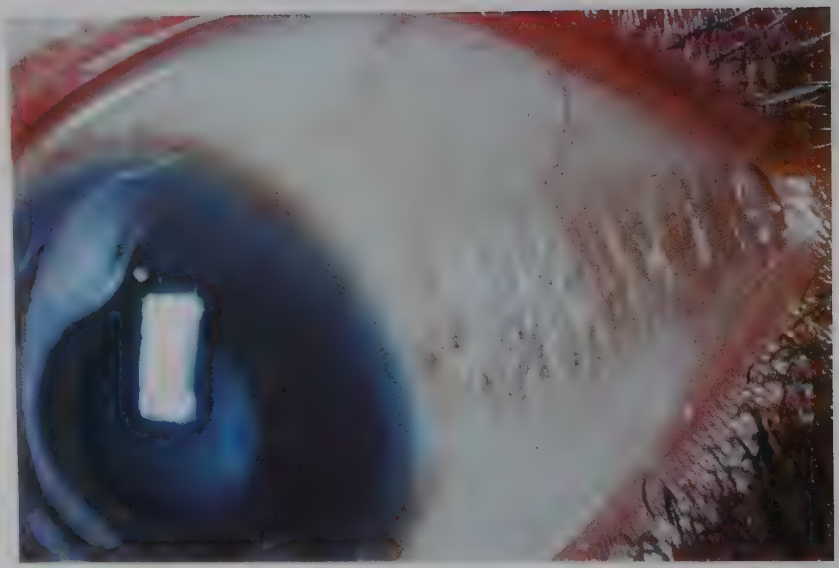


Fig. 11. X1B ("foamy")

Fig. 12. X1B ("cheesy")

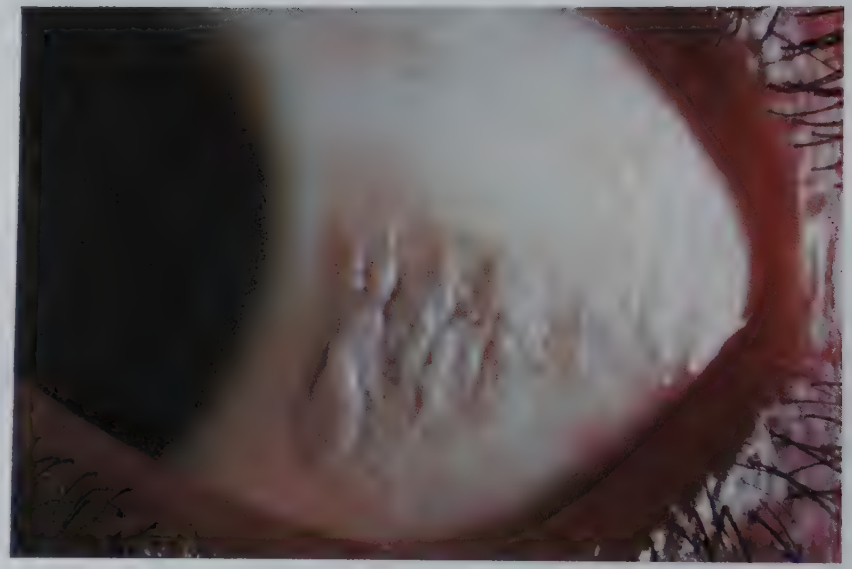


Fig. 13. X1B ("cheesy")

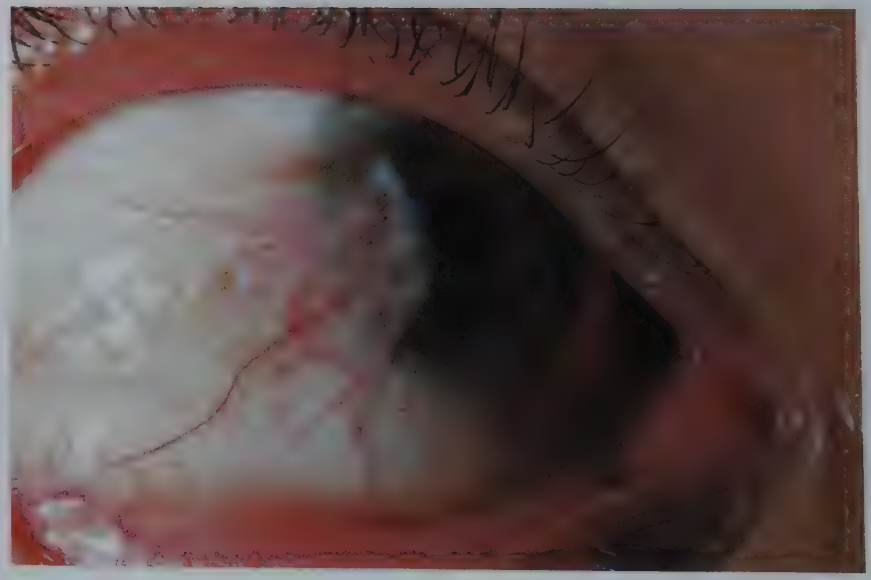
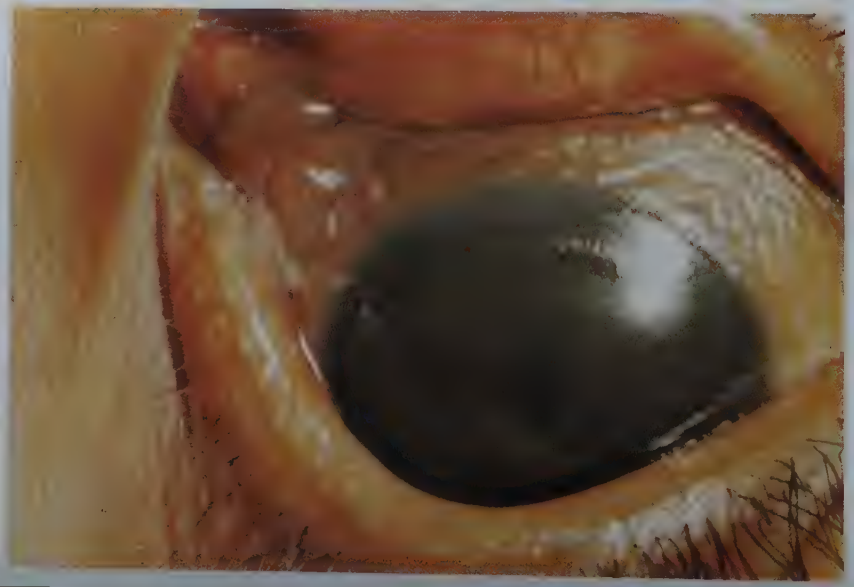
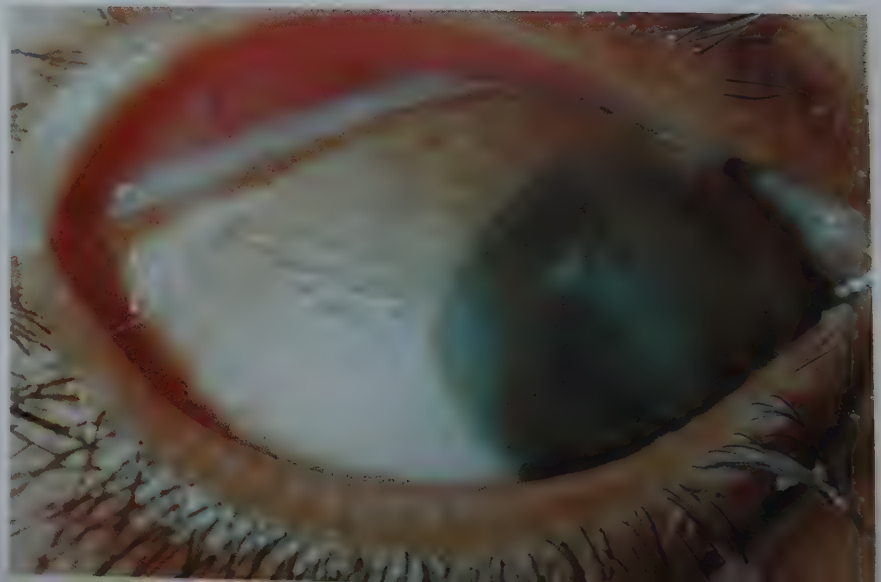


Fig. 14. Pterygium





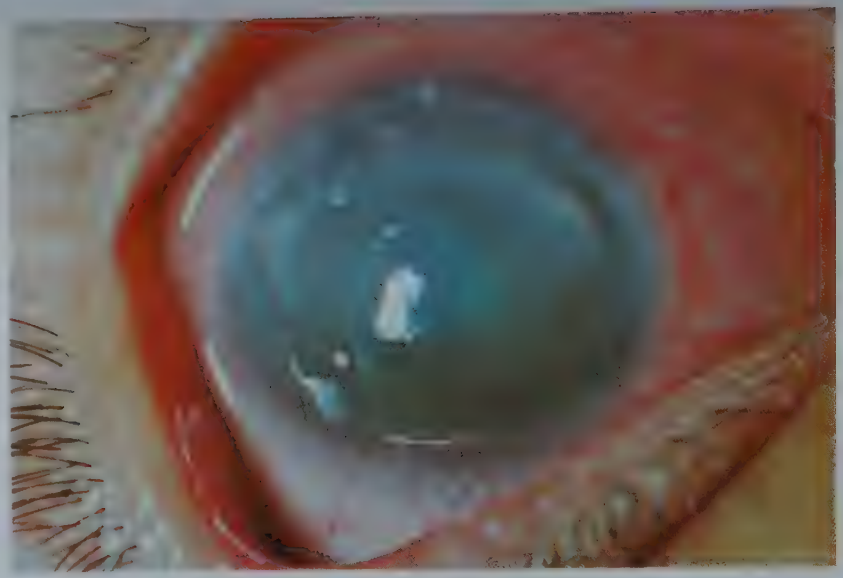


Fig. 17. X2 (haze)

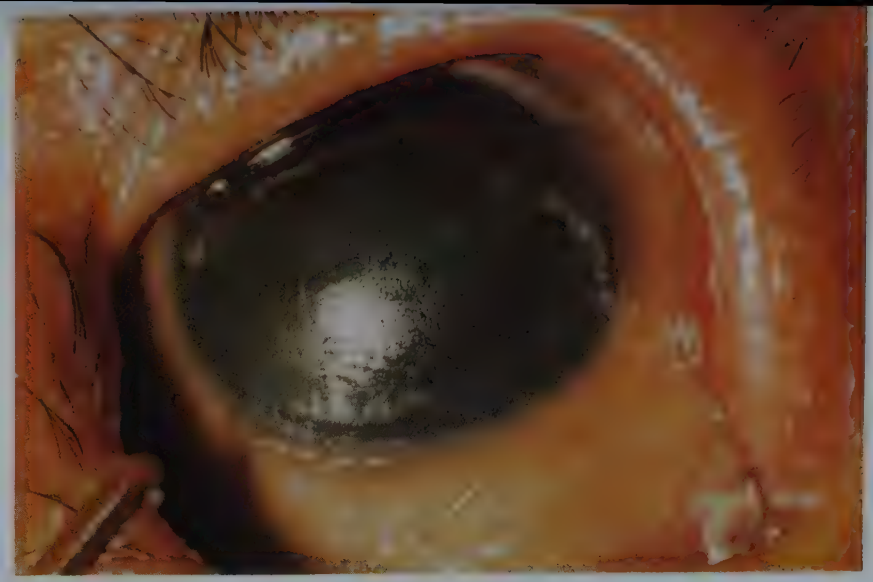


Fig. 18. X1A, X2

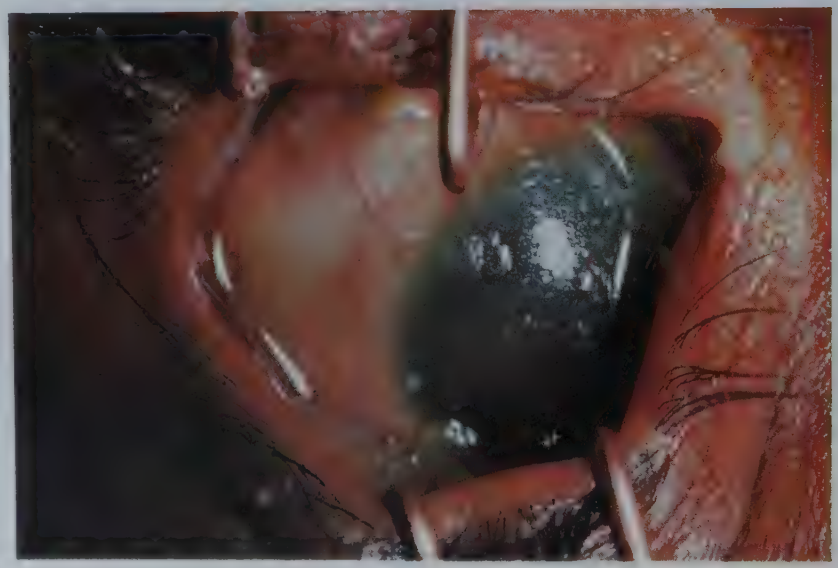


Fig. 19. X2

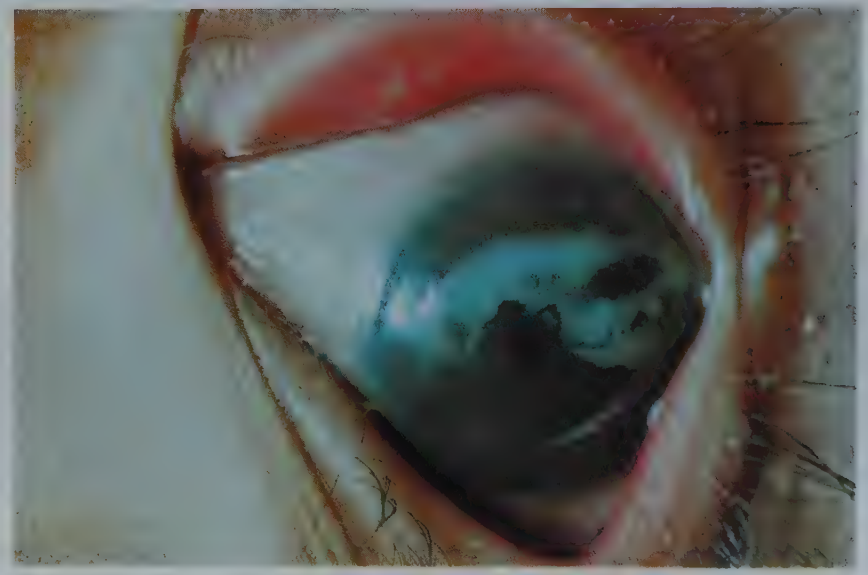


Fig. 20. X1A, X2 (with tenacious "foam")

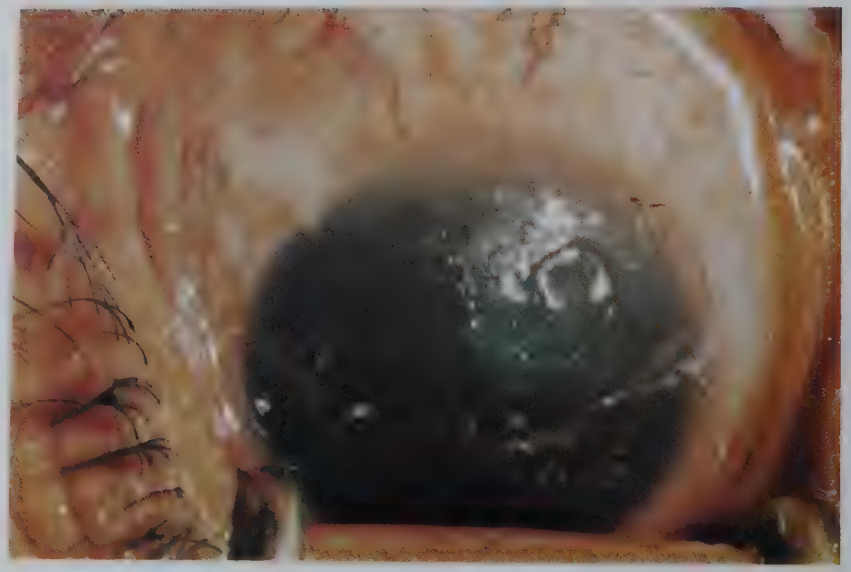


Fig. 21. X1A, X3A

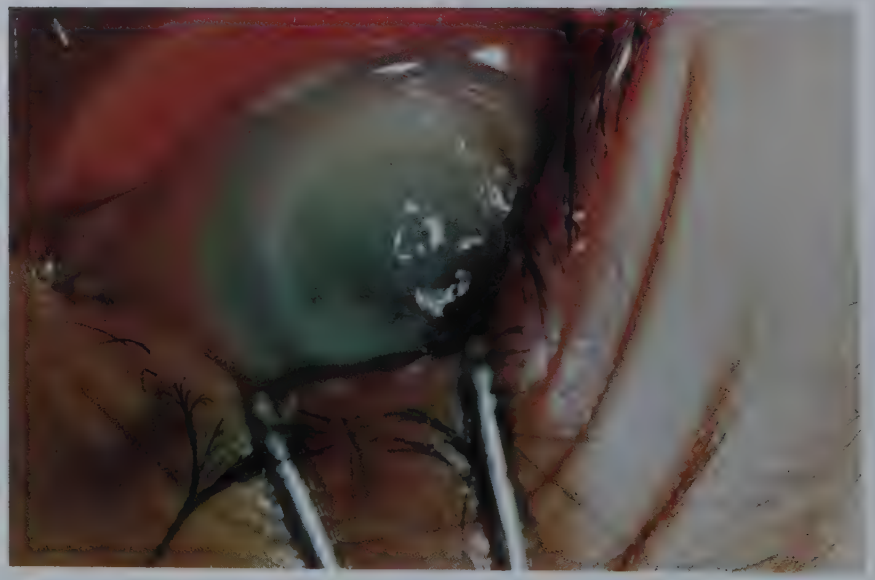
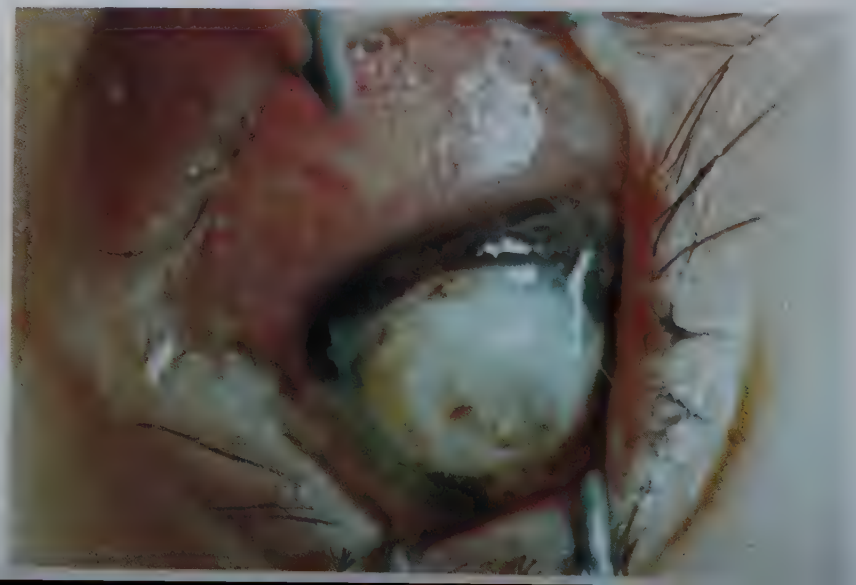


Fig. 22. X1B, X3B (generalized)



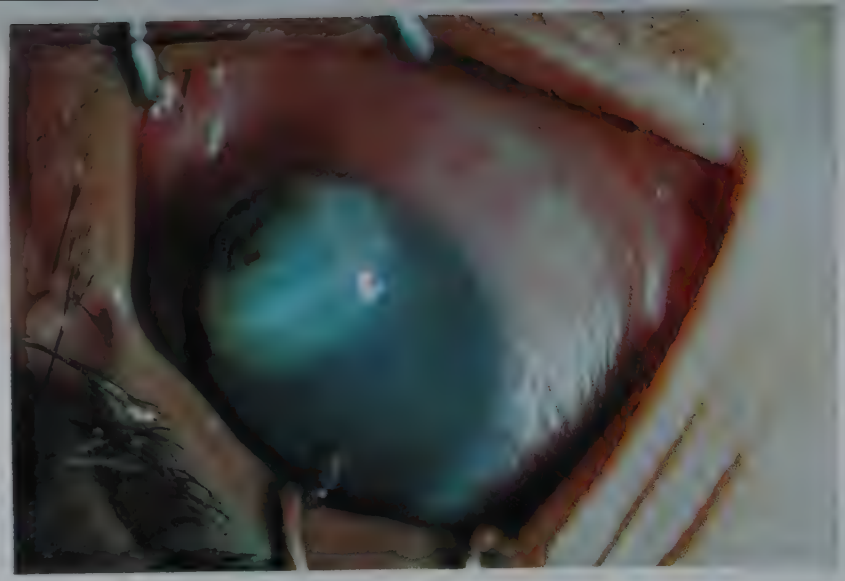


Fig. 25. X1B, X3B (localized)

Fig. 26. XS (adherent leucoma)

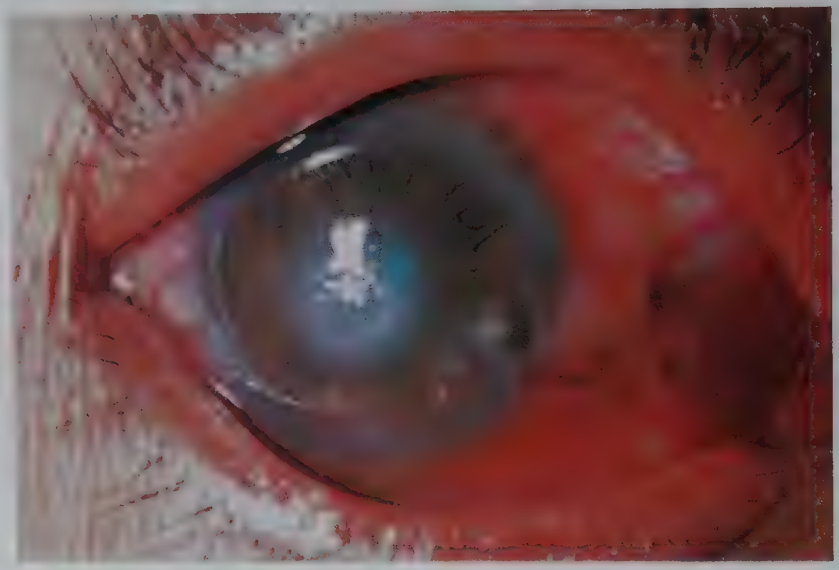


Fig. 27. Keratitis

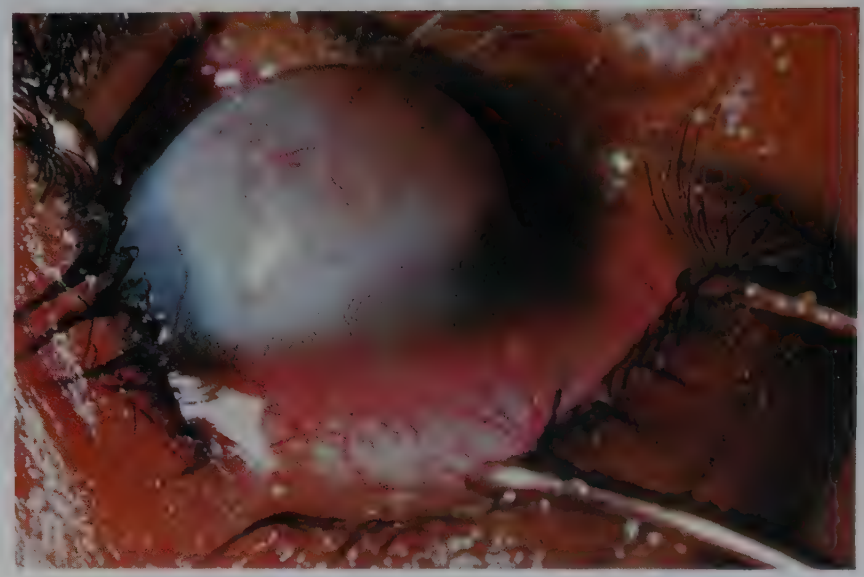


Fig. 28. XS (staphyloma)

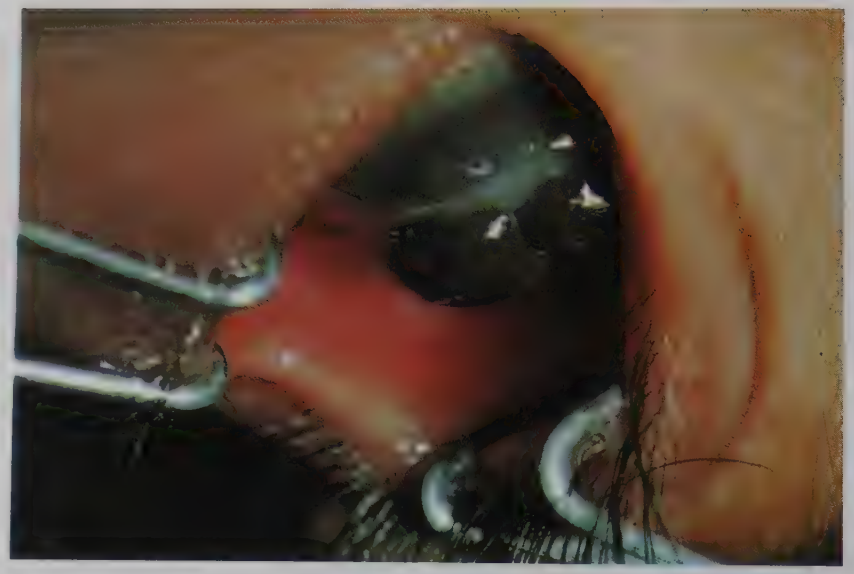


Fig. 29. XS (descemetocele)

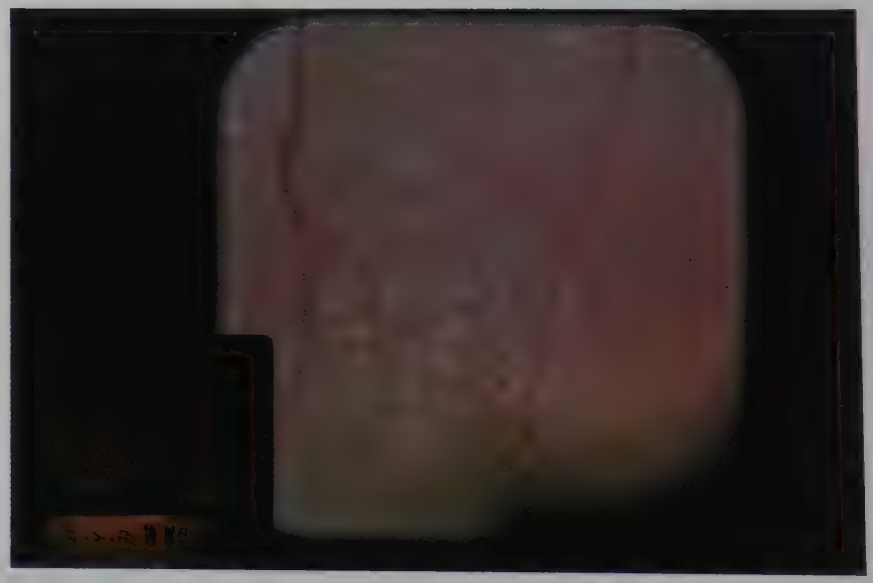


Fig. 30. XF

ASSESSMENT AND CHARACTERIZATION OF THE PROBLEM

THE formulation of an effective intervention programme begins with the characterization of the problem. Although costly and time-consuming, assessment is far less expensive than intervention itself, may indicate that the problem is much more limited than originally anticipated, and may suggest where and how prevention activities can best be applied.

When clinicians, nutritionists, or public health officials suspect the existence of a xerophthalmia problem, case-finding by local or outside experts will determine whether or not the disease actually occurs in the community under question. If it does, prevalence surveys are needed to determine its nature, magnitude, severity, and geographical distribution.

Preliminary assessment and case-finding

The search for active or healed cases of xerophthalmia should be conducted by someone experienced in the clinical recognition of the disease and knowledgeable about its pathophysiology and nutritional determinants. Ideally, this should be someone from outside the area concerned. Local specialists may mistakenly believe xerophthalmia is not a significant problem: they may not encounter the disease, because it occurs in areas or socioeconomic groups not making use of their services; or they may misdiagnose it. On the other hand, misdiagnosis or a biased referral pattern may lead them to believe it is a serious problem, when in fact it is not. The outside expert provides a fresh, impartial viewpoint backed by experience in similar situations elsewhere.

Cases should be sought in those areas where they are most likely to occur: slums and impoverished villages; ophthalmic, malnutrition, and infectious disease wards of paediatric services; rehabilitation and feeding centres; and refugee camps, orphanages, and the like. Careful, written records are more likely to be accurate than verbal "guesstimates", and direct observation of active cases is the surest means of documenting the

occurrence of the disease and the validity of past diagnosis and historical data.

Where examination, chart review, or interviews are positive, data should be collected on age, sex, seasonality, geographical distribution, and presence of antecedent or concomittant illnesses. This will be useful in designing the definitive prevalence survey.

An orderly, comprehensive, preliminary investigation should include the following:

(*a*) *Interviews*, preferably by structured questionnaire, with individuals likely to be aware of the problem: central and provincial public health officials; clinicians, nutritionists, and community health workers; directors and the staffs of hospitals, feeding and rehabilitation centres, and schools for the blind.

(*b*) *Chart reviews* at institutions where the disease is recognized or children are known or suspected to suffer from corneal destruction: clinics and rehabilitation centres, schools for the blind, and hospitals, where one may review all charts on children coded, according to the International Classification of Diseases, for diseases likely to be accompanied by, or mistaken for, xerophthalmia (conjunctivitis, keratitis, blindness, malnutrition, measles, gastroenteritis) or, where coded charts do not exist, records from the malnutrition, infectious disease, paediatric, and ophthalmic services. The conduct and interpretation of such reviews, however, are often hampered by vagaries and inconsistencies in record-keeping and retrieval.

(*c*) *Search for clinically active cases* among children at high risk: those attending clinics and feeding centres; admitted to ophthalmic, nutrition, infectious disease, and general paediatric wards; or residing in urban slums or impoverished rural communities.

(*d*) *Search for old healed disease*, with histories compatible with prior xerophthalmia (X2, X3) in schools for the blind, low-income urban areas, and in the countryside.

(*e*) *Collect existing data on dietary intake and serum vitamin A levels* for the population and presumed active cases. Where available, such data provide strong corroborative support for this diagnosis of active disease and the *potential* presence of the problem in the population as a whole.

Prevalence surveys

Prevalence surveys determine the proportion of individuals in the sample with a particular attribute or abnormality at the time of examination—*prevalence*—and provide a basis for estimating the frequency with which new, irreversible lesions are likely to occur over a given period of time—*incidence*—(see section on interpretation, page 28). When the

sample is carefully chosen to be representative of the population under consideration, prevalence rates within the sample are representative of those within the population as well.

Prevalence surveys are complex, expensive, and time-consuming. In general, they need be undertaken only where preliminary investigations indicate the presence of a potentially significant problem. Surveys containing clinical, biochemical, and dietary components are the most efficient and definitive (unbiased) means of:

(*a*) establishing the nature, magnitude, severity, and geographical distribution of xerophthalmia;

(*b*) determining whether it constitutes a significant public health problem;

(*c*) selecting suitable strategies for intervention;

(*d*) providing a baseline for evaluating the effectiveness of future intervention programmes.

Clinical parameters

Only some of the clinical signs of xerophthalmia are sufficiently objective and easily recognized to be useful in the definitive prevalence survey:

(*a*) *Conjunctival xerosis and Bitot's spots (X1B)*

These are easily recognized and relatively specific markers of active vitamin A deficiency, at least among preschool children, and are more prevalent than corneal disease. But they do not provide any information on the magnitude or extent of ocular destruction and blindness. Areas with similar Bitot's spot prevalence have widely varying levels of corneal destruction, and *vice versa*.

(*b*) *Active corneal lesions (X2, X3A, X3B)*

Corneal xerosis (with or without ulcers) and keratomalacia are the severest forms of vitamin A deficiency, and the *raison d'être* of most intervention programmes. Easily diagnosed and highly specific, these are relatively rare and rapidly progressive. Their prevalence therefore is usually extremely low.

(*c*) *Inactive corneal lesions (XS)*

Although it is difficult to assess the prevalence of active corneal disease, one can assess the prevalence of its sequelae: corneal scars and ocular destruction. It is important to distinguish between those cases likely to be the result of vitamin A deficiency and those due to other causes. This requires a careful examination, a detailed history from a responsible adult, and interpretation by an ophthalmologist.

The following diagnostic criteria are on the cautious side and would undoubtedly disqualify some lesions actually due to vitamin A deficiency. But they make it possible to be more certain of the *minimum* prevalence:

(*a*) a clinical picture compatible with that of the disease;

(*b*) the absence of other forms of disease that could have produced a similar picture (intraocular foreign bodies, advanced trachoma, etc.);

(*c*) the fact that the child was at least 4 months old when he acquired the lesion (this eliminates most congenital abnormalities and cases of neonatal ophthalmia);

(*d*) no association between the lesion's appearance and trauma, gross purulence, or measles.[1]

A history of malnutrition, respiratory infection, or gastroenteritis concomitant with the onset of the lesion supports the diagnosis.

If the history is either vague or unavailable, this should be stated, and the cases reported under different categories: "possibly", or "unlikely" to be, the result of xerophthalmia, depending upon the clinical picture. Other causes of corneal destruction should also be tabulated, e.g., congenital, traumatic, arising from infection, associated with measles, etc.

Although the diagnosis of xerophthalmia-related corneal destruction is retrospective, few if any other conditions produce significant numbers of cases with a similar clinical and historical pattern. Since only survivors are examined, the observed *prevalence* (frequency of cases in the population at any one time) of sequelae gives an inadequate idea of the *incidence* (number of *new* cases in the community over a given period of time) of active disease. Suggestions for examining children in the field are presented in Appendix 1.

Biochemical parameters

Despite the fact that active xerophthalmia is usually associated with low serum retinol (vitamin A) levels, the relationship is insufficiently fixed and precise to permit the level of clinical disease to be estimated from biochemical data alone. As part of a clinical prevalence survey, however, serum retinol levels for "abnormals", "controls" (see page 36), and a random or a systematic subsample of the study population (every twentieth child) can provide important insights into the distribution of the disease.

Low serum retinol levels for "abnormals" (children with active xerophthalmia, X1B-X3B) provide independent corroboration of the clinical diagnosis.

[1] Measles may simply be another precipitating factor in vitamin A deficiency. But the association is still controversial, and measles-associated cases should be listed and tabulated separately.

Serum retinol determinations on the random subsample establish the degree of subclinical vitamin A deficiency in the community. Where retinol levels are generally low, approaching those for "abnormals", vitamin A deficiency is widespread and the community as a whole at risk of clinical disease. Where they are high, however, the community as a whole is relatively normal, and vitamin A deficiency and the potential for clinical disease are relatively infrequent. How infrequent they are may be determined from the serum levels among controls. If these approach the relatively normal levels of the random subsample, the potential for disease is limited to those few individuals already having active xerophthalmia. On the other hand, if the levels are more like those among the "abnormals", then the potential for disease is more widespread, confined not to individual children but to neighbourhoods or localities, especially those in which the "abnormals" reside.

Biochemical components should be included only where adequate facilities exist for the collection, storage, and transport of samples, and where equipment and expertise exist within the country or arrangements have been made with a reference laboratory outside the country to carry out the determinations. Suggestions for collecting and handling blood specimens in the field are discussed in Appendix 1.

Dietary parameters

Like serum retinol levels, dietary histories cannot determine the prevalence or severity of xerophthalmia in the community. An understanding of food consumption patterns of children with active xerophthalmia and their families is, however, indispensable for determining why these children became deficient in vitamin A, selecting a vehicle for vitamin A fortification, and designing appropriate messages for health education programmes.

Three different sets of forms may be used: a family-based qualitative history to determine the frequency with which different foods are eaten by the family, as a whole, and where these foods were procured; a similar form for individual children, which includes, in addition, questions on breast-feeding and weaning practices; and a quantitative history which attempts to determine the exact quantity of each food eaten by the child during the past 24 hours. For comparison, forms are completed on all "abnormal" children, their matched controls, and a random or a systematic subsample of all children (every twentieth child) examined, and their respective families. Where children do not eat foods that constitute sources of vitamin or provitamin A, it is important to enquire about the reasons (e.g., they are expensive, locally unavailable, not considered healthy for children, the child does not like them, etc.).

The list of foods should include all locally available major sources of vitamin and provitamin A, potentially fortifiable foodstuffs, staple foods, and major sources of protein.

Qualitative data can usually be collected by a suitably trained field worker, but quantitative data require a trained nutritionist, samples of the foods under consideration, and scales to weigh the amounts the child consumes, as indicated by the mother.

Sample forms are given in Appendix 2.

Preparatory data

Rough estimates of the magnitude and seasonal variations of the problem will be useful in choosing the sample size and timing the survey for the period of maximum prevalence. Such data should already be available from the preliminary assessment.

The factors involved in selecting a suitable sample are discussed below. The actual procedure employed, however, will vary from survey to survey, depending upon local conditions and interests, and it should be determined by an epidemiologist or statistician experienced in sampling design.

Sample size

Ideally it would be preferable to survey the entire population, but this is rarely practicable. In choosing a sample instead, the size will depend upon the expected prevalence of the least common (rarest) clinical criterion and the precision desired. The greater the precision and the lower the expected prevalence, the larger the sample required. As an obvious example, a condition that occurs in one out of every 10 children requires a far smaller sample than one that occurs in one out of every 10 000 children, for equal levels of precision.

A simple prevalence rate in a sample population is almost meaningless. There is no assurance that it accurately reflects the true prevalence in the community at large. Such an assurance is gained by bracketing this figure with "confidence limits", which express a certain known probability of including, between them, the "true" prevalence. One commonly uses the detected prevalence plus or minus 2 standard errors. The "true" prevalence then has a 95 % probability of lying somewhere within the bracketed range.

"Expected prevalence" can be estimated from existing data, or by employing the suggested minimum criteria for levels representing a public health problem (see Table 4, page 29) or any other level of disease that the government considers sufficient to justify an intervention programme.

The clinical prevalence survey should provide an estimate of the magnitude of corneal destruction related to vitamin A deficiency. Healed sequelae (XS), the only evidence of such destruction that usually occurs in sufficient quantities to make such estimates practicable, requires a sample size of at least 5000–10 000 children (using the suggested minimum criterion of a level of 0.1 %). Since the corroborative biochemical criterion for vitamin A deficiency and xerophthalmia as a public health problem is severely depressed serum retinol (vitamin A) levels in 5 % of the population, a far higher prevalence than that of corneal scars, only one out of every 20 children undergoing clinical examination need be sampled.

Comparisons between different regions require a complete survey of adequate sample size in each.

Selection of sample

Selection begins by defining the "population at risk", i.e., that segment of the community in which xerophthalmia is thought to occur and from which the sample will be drawn. Individuals over the age of 6 and upper- and middle-class families rarely develop xerophthalmia and are usually excluded. Results will then apply only to preschool-age children from low-income families. Since these include the vast majority of cases, estimates for the entire population of preschool-age children are developed by multiplying the prevalence in the "at risk", sampled group by the proportion of all preschool-age children they represent. For example, if 50 % of preschool-age children are at risk, and the prevalence of scars related to vitamin A deficiency in the sample drawn from this group is 2 per 1000, the estimated prevalence for the entire population of preschool age is 1 per 1000. The urban sample can be limited to slum dwellers as long as they account for the bulk of urban xerophthalmia and the proportion of the urban population living in slums is known.

Every individual in the population at risk must have a fixed, known probability of being chosen for the sample; otherwise it will not be possible to carry out the statistical manipulations necessary for estimating means, prevalence, and standard deviations in the population. Limiting the sample to "captive", accessible children in hospitals, clinics, schools, and day-care centres is inappropriate. The probability of entering the sample is very different for these children than for others, and they are not representative of the population.

Stratified, multistage, cluster sampling is the most practical and popular means of sampling the population at risk. Instead of examining children scattered at random throughout the population—a logistical nightmare—small geographical or administrative units (clusters) are chosen in which all children or a large sample of them are examined. The larger the number of clusters, the more representative the sample.

The size of the clusters is usually limited to the number of children a team can examine in a day: roughly 100 per rural cluster and two to four times as many in densely populated urban slums.

Sampling accuracy is improved and useful comparisons often made possible by *stratifying* the population into "like groups" (e.g., urban/rural, mountain/seaside, dry belt/wet belt, and even high/low or unknown risk of disease) and choosing the clusters from within each stratum separately. Population-wide calculations are simplified if the number of clusters chosen from each stratum is proportional to the size of the stratum. If 40 % of the group at risk live in urban areas, 40 % of the sample is drawn from such areas. Alternatively, equal samples can be drawn from each stratum and then weighted accordingly. In the example above, the prevalence in the urban stratum would be multiplied by 0.4, that in the rural stratum by 0.6, and the two products added.

Sample clusters can be chosen from a list (sampling frame) composed of all cluster-size units within the stratum. *Multistage* sampling is usually simpler. In the first stage, the stratum is divided into relatively large administrative units (e.g., districts), and the number of clusters (if any) to be contributed by each determined. In the next stage, every subunit (e.g., village) in the selected district is listed, and the number of clusters (if any) to be contributed by each determined. The process is repeated until the final, cluster-size units (perhaps neighbourhoods) are selected. In the early stages at least, the probability of selecting the units should be proportional to their size. This ensures a more representative sample and eliminates the need for weighting factors in calculating stratum-wide results.

In practice, it is rarely necessary to go through this entire process. Other groups involved in survey work within the country (census bureaux, demographic and family planning units, social research institutions, etc.) will often have developed samples for their own purposes, complete with cluster maps, family registers, etc., that can be adopted with little if any modification. If not, census bureaux, malaria control programmes, etc. can at least provide a list of administrative units and the rough population estimates necessary for constructing the sampling frames.

Field teams must rigorously adhere to the selected sample, and any deviation must be analysed for bias. Occasionally a selected site cannot be found or reached within a reasonable period of time and must be dropped. But if the field team consistently ignores remote sites, the sample ceases to represent the entire population at risk and reflects instead only the accessible portion.

Forms

The clinical examination and questionnaire should be as limited as possible. The more observations to be made and questions asked, the

greater the likelihood that each will be dealt with superficially and carelessly. Depending upon local interests and capabilities, however, ancillary data and special studies on *subsamples* of the study population can provide unique epidemiological information and greatly enhance the value of the survey. Serum retinol (vitamin A) levels, dietary histories, socioeconomic data (e.g., educational level of the parents, size of the family, source of drinking-water, means of lighting the house at night, material used in construction of the house, employment status of adults, etc.), and anthropometric measurements (weight or arm circumference for height) on a random subsample and on "abnormals" and age/sex/locality-matched non-xerophthalmic controls are but some examples.

All pathological conditions referred to should be easily recognizable and the criteria for them should be clear-cut and reproducible. All questions must be clear, objective, and amenable to simple codable responses. It is always useful to review all questions, especially of a socioeconomic nature, with rural sociologists or others who have had previous experience in the area, retaining only those which the population is likely to answer reliably. For example, direct, specific questions on land-holding and income are rarely answered properly or truthfully.

All questions should be phrased in the basic working language of the field team, as well as in any local languages or dialects likely to be encountered. Field forms designed and precoded for direct transfer to 80-column IBM punch cards will speed and simplify the analysis. All forms should be reviewed at least twice for legibility, accuracy, and completeness before being forwarded for card-punching, and all punch cards should be *verified*.

Forms and teams require one to two weeks' pre-testing in the field before the forms are finalized or any sample sites visited. Ambiguous questions can be changed or eliminated, interview techniques standardized, and poor-quality, unenthusiastic workers replaced.

Sample forms are provided in Appendix 2. The summation coding format is employed wherever possible to maintain discrete information while economizing on punch-card columns.

Personnel and field activities

Depending upon the size and complexity of the survey, a number of different specialists will be required:

1. *An epidemiologist* to design the survey, monitor its progress, and analyse the results. If he is not fully competent in statistical matters, a statistician will be needed as well.

2. *A clinician*, knowledgeable in the diagnosis of xerophthalmia, to conduct all ocular examinations. Ophthalmologists, through experience and training, are best equipped to recognize the milder conjunctival

lesions, differentiate between various causes of corneal scarring, and recognize concomitant and possibly contributory ocular abnormalities. Where more than one clinician is involved their respective performances must be rigorously and repeatedly compared to ensure uniformity and, in all instances, correlated with that of an outside expert. Whenever possible, all ocular abnormalities should be photographed. This is a useful means of validating the reproducibility and standardization of the observations.[1]

3. *A nutritionist* to collect all dietary histories and supervise anthropometric measurements.

4. *A biochemist* to oversee the collection and handling of blood specimens.

5. *An outside expert, if possible, who has participated in similar surveys in other countries* to advise the team and standardize its work methods.

Each field team is commonly composed of an ophthalmologist, a nutritionist (where dietary histories are included), two nurses, four trained field workers (enumerators), and, whenever possible, an additional individual to arrange administrative, logistic, and financial matters.

Teams should spend at least two weeks familiarizing themselves with the forms and procedures, at first in a hospital or clinic and later in the field, before ever visiting the first sample site. Nurses and enumerators should be taught interview techniques and the various means of determining a child's age (relating his birth to major events in the community, his siblings, etc.). Field practice begins slowly, with one enumerator interviewing a family while the others watch. In this way they overcome their reticence and learn from one another's mistakes. As their confidence and skill increase they can interview families on their own, with the epidemiologist and nutritionist periodically checking their performance. Once the team is working smoothly at full capacity, it is ready to visit the sample sites and begin the survey.

Whenever possible, site visits should be timed to find the largest number of preschool children at home: villages should not be visited on market day or while mothers are out in the fields.

Enumerators visit every house in the cluster and keep a careful record of those that are empty, do not contain eligible children, or contain eligible children who were away at the time or whose parents refused to cooperate. Such data are important in evaluating the results for bias. If large numbers of families with eligible children are away in the fields or will not cooperate, it is reasonable to suppose that their characteristics

[1] The Kodak 5-SK Dental Kit is a simple, inexpensive macro-lens camera, suitable for field use.

and risk of xerophthalmia might well be different from those of families that were examined.

The enumerator completes a form on all cooperating families with eligible children, filling in basic socioeconomic data and listing and identifying all eligible children, later assembling them at a central point for examination. House-to-house visits are the only means of avoiding the bias of "volunteer" samples and of assessing the magnitude of the potential bias created by absent children.

The supervisory nurse has at least three tasks: checking the accuracy of the enumerators by re-interviewing 10 % of the mothers; conducting anthropometric measurements and collecting blood samples when these are included; and assisting the ophthalmologist, when necessary, in examining the child.

Whenever more than one team is involved in the survey, they should all work in the same general area, rather than widely separated regions. Otherwise regional differences may be ascribed (rightly or wrongly) to differences in the teams.

All children with serious illness or evidence of xerophthalmia should receive appropriate therapy (Table 3).

Table 3. Vitamin A dosage schedule

Condition	Therapy
	Immediate therapy
Active xerophthalmia	Water-based vitamin A in the amount of 55 mg retinol palmitate (100 000 IU) intramuscularly
or	or
	(less acceptable)
Severe malnutrition or illness in areas where xerophthalmia occurs, whether or not patient shows evidence of clinical disease	55 mg retinol palmitate (100 000 IU vitamin A) < 12 months old 110 mg (200 000 IU) ⩾ 12 months old orally in water or oil
	The following day
	55 mg retinol palmitate (100 000 IU vitamin A) < 12 months old 110 mg (200 000 IU) ⩾ 12 months old orally in water or oil
	Prior to discharge [a]
	55 mg retinol palmitate (100 000 IU vitamin A) <12 months old 110 mg (200 000 IU) ⩾ 12 months old orally in water or oil Repeat at intervals of 1–6 months

[a] This schedule is also applicable in the case of lactating mothers and children aged 0–6 years attending clinics, etc.

Data analysis

Background data should include maps and tables indicating the location and number of selected sites and those that were actually visited, as

well as the number of children anticipated, the number present, and the number and proportion actually examined in each stratum by age (years completed) and sex. This orients the reader and facilitates the search for bias.

Clinical findings should be reported in accordance with the xerophthalmia classification given in Table 1 (page 11), and each child with *active* disease included only once, under his or her most severe sign (X3B, X3A, X2, X1B). In addition, note the proportion with old, healed corneal disease (XS). Tabulations organized by age and sex within each stratum, indicating the number of "abnormal" children and the prevalence (rate per 1000) for each sign, facilitate the construction of age-, sex-, and stratum-specific rates, overall survey rates, and corresponding confidence limits, as well as the search for clinically and epidemiologically important differences. The statistical significance of these differences should be determined.

The proportion of cases of corneal xerophthalmia with bilateral involvement and monocular and binocular blindness, and the age, sex, and geographical distribution of patients with other causes of corneal damage are of interest.

Serum retinol (vitamin A) levels should be reported separately for "abnormals", controls, and the random or systematic subsample. "Abnormals" or controls originally chosen as part of the subsample, prior to their clinical classification, remain so and should be included in both categories.

The frequency distribution (within steps of 100 μg/l or 0.35 μmol/l), mean, standard deviation, confidence limits, number of eligible children, and number of specimens collected and analysed should be tabulated for each category. Wherever possible, the data should be age-, sex-, and stratum-specific. Values for the random subsample reflect the vitamin A status of the population from which the original clinical sample was drawn.

Qualitative *dietary* patterns of children with active xerophthalmia are reported separately from those of their families. Tabulate the source and frequency of consumption of each major class of foods and individual items of particular importance (those rich in vitamin or provitamin A, or potentially fortifiable).

Interpretation

The clinical prevalence survey documents the magnitude and geographical distribution of xerophthalmia in the area under investigation. Administrative leaders must then determine whether, and where, the problem is sufficiently serious to warrant intervention. Criteria for the community diagnosis of xerophthalmia and vitamin A deficiency at

levels considered to represent a significant public health problem have been proposed to assist government administrators in this task (Table 4). These apply only to children up to the age of 5 years in the area actually surveyed. The presence of one or more of the three *clinical* criteria should be considered as evidence of a significant xerophthalmia problem. The biochemical criterion is strong corroborative evidence of any clinical criteria met. Only the criteria for *corneal disease* (X2, X3, XS) indicate serious ocular problems that might possibly lead to blindness.

Table 4. Community diagnosis of xerophthalmia and vitamin A deficiency

Criterion	Minimum prevalence
Clinical	
Conjunctival xerosis with Bitot's spot (X1B)	2.0 %
Corneal xerosis and/or keratomalacia (X2 + X3A + X3B)	0.01 %
Xerophthalmia-related corneal scars (XS)	0.1 %
Biochemical	
Serum retinol (vitamin A) less than 100 μg/l (0.35 μmol/l)	5.0 %

To make a rough estimate of the number of children each year who develop new corneal destruction related to vitamin A deficiency, one should multiply the prevalence of corneal scars related to vitamin A deficiency (XS) among 5-year-olds by the total number of 2-year-olds (the median "at-risk" age group) in the region (or country) under study. Because the number of cases of XS observed in the survey is likely to be small, the chance variation in prevalence between adjacent age groups may be substantial. Thus a more accurate, if conservative, estimate is usually obtained by using the overall prevalence among 4- or 5-year-olds in the sample instead, as shown below:

$$\frac{\text{Cases of XS among 4- and 5-year-olds in sample}}{\text{Number of 4- and 5-year-olds in sample}} \times \text{Total population of 2-year-olds} = \text{Number of new surviving cases of XS each year}$$

In most instances a quarter of these children will be bilaterally blind. Since the survey enumerates surviving cases and mortality is usually estimated at 50 %, the true incidence is probably at least twice this rate. In some areas mortality surpasses 90%, and the true incidence is therefore correspondingly higher.

These criteria should not be interpreted rigidly. They are only guidelines, to be interpreted in the light of existing health resources and competing priorities. They should be compared with the overall rates and with the rates in specific, high-prevalence areas, and intervention programmes targeted accordingly.

TREATMENT

EFFECTIVE therapy requires prompt recognition of children with, or at high risk of developing, active disease; immediate administration of massive doses of vitamin A with concomitant treatment of underlying systemic illnesses; and prevention of any recurrence.

All children at risk of corneal destruction related to vitamin A deficiency must be promptly identified. These include:

(*a*) those who already have evidence of active xerophthalmia (XN–X3B);

(*b*) severely ill and malnourished children coming from communities where xerophthalmia is known to occur, whether or not they themselves already have clinical evidence of vitamin A deficiency.

This is a medical emergency, requiring the prompt administration of massive amounts of vitamin A. The vitamin can be administered orally or parenterally. Parenteral administration is preferred in all cases with active disease, or where severe malnutrition or systemic illness might interfere with intestinal absorption (Table 3).

Inject *water-based* vitamin A intramuscularly in the amount of 55 mg retinol palmitate (100 000 IU). Oil-based preparations are liberated extremely slowly from the injection site and should never be used. Where water-based parenteral vitamin A is unavailable, administer 110 mg retinol palmitate (200 000 IU of vitamin A), in water or oil, by mouth. In either instance, an additional 110 mg (200 000 IU) should be administered by mouth the following day, to ensure adequate treatment and boost liver reserves. The doses should be reduced by half for children less than 1 year old.

In the presence of corneal involvement, apply broad-spectrum antibiotic eye ointment every 8 hours to reduce the risk of secondary bacterial infection. As always, established infections require immediate, vigorous local and systemic therapy. Until such time as the responsible agent is identified, antibiotics should be chosen to cover a wide range of organisms, especially *Staphylococcus* and *Pseudomonas* (e.g., topical bacitracin and gentamicin, plus subconjunctival and systemic gentamicin and meticillin).

Every effort should be made to preserve the structural integrity of the globe. Eyes with weakened corneas (active keratomalacia, ulceration, or thinning) must be protected from undue pressure: examinations, applications of drugs, and dressing changes should be done with the utmost care, and the eye covered, at all other times, by a firm plastic or metal shield. When necessary, the child's hands can be restrained.

Proper attention should be given to correcting underlying protein-energy malnutrition and systemic illnesses. Prior to discharge from the hospital, clinic, or rehabilitative centre, administer an additional dose of vitamin A orally — 55 mg retinol palmitate (100 000 IU) to those under the age of 1 year, and 110 mg (200 000 IU) to those who are older. This should ensure protection for 2–6 months.

Where vitamin A preparations are not yet available, treatment should be instituted with foods rich in vitamin A (meat and dairy products, fish liver oil, etc.) or β-carotene (green leafy vegetables, including leaves of the Drumstick or Horseradish Tree (*Moringa oleifera*), cassava leaves, etc., red palm oil, and red, yellow, and orange coloured fruits, such as papaya and mango). A small amount of edible oil will enhance the absorption of the β-carotene.

Preventing recurrence

The vulnerable children have already demonstrated that their home environment is deficient in vitamin A. Their mothers need to be taught the necessity of providing diets rich in vitamin A and shown how to prepare them from inexpensive, readily available sources (primarily green leafy vegetables). As a rough estimate, 40 g of green or red varieties of amaranth, 35 g of drumstick leaves, or 100 g of mango all provide the daily requirements for toddlers and preschool children. Large, simple wall posters in clinic and hospital waiting-rooms will alert mothers to the problem and its prevention. Nutritionists, dietitians, and other specially trained personnel can instruct those with affected children in greater depth. Periodic follow-up will ensure that xerophthalmia has not recurred and, where it has, provide the opportunity for prompt treatment. Administration of massive-dose capsules (appropriate for age) at 4–6-monthly intervals will ensure that the child has adequate vitamin A stores.

Prompt and effective therapy requires parenteral and oral vitamin A preparations to be available at all hospitals, clinics, health units, and rehabilitation centres likely to encounter the disease. Standardized 100 000 and 200 000 IU capsules of vitamin A are cheap, increasingly available, and perfectly safe when given in the recommended amounts. Larger doses or overfrequent administration may be toxic, however,

resulting in headaches, vomiting, seizures, changes in mental activity, and other evidence of increased intracranial pressure.

Prompt and effective therapy also requires doctors, nurses, and paramedical personnel trained in the recognition and treatment of the disease. These last should be included in the basic curricula of all schools of medicine, nursing, and paramedical training, and short courses should be held for those already in practice. A series of simple, inexpensive teaching guides on the subject have been produced for individuals of varying professional skills (see bibliography). One set of teaching guides should be left at each treatment centre for future reference.

PREVENTION

The ultimate goal of any prevention programme must be the regular, adequate dietary intake of vitamin and provitamin A by vulnerable children, and the elimination of all forms of vitamin A deficiency. But this is a long-range task. In the interim, short-term, necessarily expensive emergency measures are needed to prevent at least that degree of vitamin A deficiency responsible for ocular destruction and blindness. How and to what extent this is accomplished will depend upon the severity and nature of the deficiency, the resources available, and the degree of dedication and desire to attack the problem. To be effective, all such programmes must reach the children at greatest risk.

An understanding of the dietary and socioeconomic determinants of xerophthalmia is necessary in order to design appropriate intervention programmes for each community. Where the necessary data have not already been collected in the course of the original prevalence survey, limited secondary investigations must be conducted in the areas of high prevalence.

At least three different forms of intervention are at present in use.

Distribution of massive-dose capsules

Vitamin A capsules containing 55 mg retinol palmitate (100 000 IU) —for children less than 1 year of age—or 110 mg (200 000 IU) for those who are older are thought to provide sufficient liver stores for 2–6 months. Although these capsules are relatively cheap, safe, and increasingly available, continued protection requires readministration at regular intervals (usually every 6 months) and the drop-out rate is often discouraging. The major cost is in the distribution itself. Where this can be accomplished through existing programmes (by antimalaria or multi-purpose community workers, village midwives, etc.) the cost is not excessive. But where entirely new, single-purpose workers need to be employed, the cost rises dramatically. Even so, a great deal can still be accomplished by ensuring that adequate stocks of capsules are available

at all clinics, health, feeding, and rehabilitation centres, and hospitals likely to encounter the disease or located in areas where xerophthalmia is known to occur. Capsules can then be administered, at low cost, to all children and pregnant and lactating mothers attending these facilities, whatever the reason (see Table 3). Care must be taken to ensure that the children do not receive the capsules too frequently (more than once a month).

It should be recognized, however, that large numbers of children will remain unprotected. Characteristically, these children are from the lowest socioeconomic strata, often reside in remote, inaccessible areas, rarely if ever make use of existing health facilities, and are at the highest risk of disease.

Fortification of food products

The addition of selected nutrients to common dietary staples is a well proven, efficient, and inexpensive means of delivering these nutrients (iodine, vitamin D, etc.) to the community. The same could be, and indeed is already being, done with vitamin A. The major problem is identifying an appropriate vehicle: a food that is widely consumed, especially by the children at the highest risk of xerophthalmia; the intake of which is relatively uniform in all segments of society where it is used, so that a properly selected concentration will deliver sufficient quantities of the nutrient to the target population without overdosing the highest consumers; and the processing of which takes place at relatively few central points where the nutrient can be conveniently added.

The qualitative dietary component of the clinical prevalence survey (or subsequent intensive investigations in high risk areas) will have identified which food items, if any, are consumed by a majority of children (or, less ideally, families of children) with active xerophthalmia and are therefore capable of reaching the target population. Additional dietary studies, on a limited number of children hospitalized with active corneal disease, will ensure that the fortified food reaches those at highest risk. The level of fortification required can be calculated from the quantitative data.

The additive should be inexpensive, stable, and virtually undetectable in the food vehicle selected. Significant changes in the cost, colour, texture, odour, or taste of the final product might discourage consumption. The pharmaceutical industry has proved most ingenious in this regard and has already developed the technology for fortifying milk, tea, sugar, cereal grains, monosodium glutamate, and a variety of other foods and seasonings. A premix, containing high concentrations of the nutrient in a form closely resembling the final product, is mixed by relatively simple feeders with the food item itself. Careful monitoring

and controls are important, especially early in the programme, to guard against under- and overdosage, settling of the premix, loss of potency, and changes in consumption patterns. The fortification of sugar with vitamin A, already under way in at least two Latin American countries, demonstrates the technical feasibility of this approach.

Health education and horticultural activities

Increased production and intake of vitamin A and carotene-rich foods are likely to be the ultimate, long-range solution to the problem.

The first step is to determine the appropriate message for each community. Socioeconomic and dietary data from the prevalence survey provide useful clues. For example, if parents of children with active disease are found to consume large quantities of foods rich in vitamin or provitamin A, but do not feed them to the children, the appropriate message will be quite different from the one that should be used if the families never consume such foods. Likewise, there is little reason to promote "home gardens" if foods rich in vitamin and provitamin A are cheap and abundant and their lack of use is primarily due to dietary preference or cultural taboo.

In some instances, an appropriate vehicle for fortification will be used by the family, but not by the child at risk. In this case both forms of intervention might be employed: fortification of the food plus an attempt at changing feeding practices.

Health education techniques themselves are undergoing considerable development. Mothers need to be taught the importance of breast-feeding and the early introduction of vitamin- and protein-rich solids, as well as methods of preparing nutritious diets for the young child even with a limited budget. Where warranted, family members need motivation and instruction in planting home gardens. These tasks have been carried out by village-level "extension" workers and by specially trained personnel addressing "captive" populations at hospitals, clinics, and rehabilitation centres (where the mothers are often directly involved in growing and preparing the foods). Mass media techniques, common in technologically advanced countries, are proving surprisingly effective in rural, agrarian societies. But educational programmes tend to spread slowly. It is therefore important that they be actively developed and encouraged, along locally appropriate lines, even while short-term emergency measures are in use.

Evaluation

Xerophthalmia prevention programmes are still in their infancy, and no method, no matter how successful in one country, is assured of

success in another. To prevent the needless expenditure and false sense of security engendered by theoretically useful, but ineffective programmes, every new programme should undergo evaluation. One should at least know whether or not it is having its desired effect.

A programme launched to prevent keratomalacia should in fact be shown to reduce corneal destruction. Measuring changes in biochemical status or the prevalence of Bitot's spots in the community is not sufficient. If, on the other hand, keratomalacia is not a significant problem and the intervention is intended to improve the general vitamin A status of the population at large, such changes are legitimate criteria for investigation.

New intervention programmes should begin as pilot projects in limited, high-risk areas. Their effectiveness can be assessed, the problems identified, and changes made before expending large amounts of time, money, and effort in what might turn out to be a useless and inefficient approach.

The effectiveness of the programme can best be determined from prevalence data, for which the assessment phase will already have provided a baseline, and from clinical records. The latter approach is simpler, but potentially biased, and requires a clinical unit that encounters and accurately recognizes and records large numbers of cases. While these criteria are rarely fulfilled, simple standardized xerophthalmia-reporting forms can easily be developed for hospitals and clinics recognizing large numbers of cases (Appendix 2). Repeated prevalence surveys are more representative of the community at large, but provide less detailed information on active corneal disease. Wherever possible, both techniques should be employed.

Comparisons are needed between populations covered and not covered by the programme. Ideally, there should be one group of participants in the pilot programme and, at the same time, a control group of non-participants. This system of *concurrent* controls ensures the most accurate comparisons. The two groups should be as much alike as possible, at least as regards socioeconomic conditions, dietary practices, ecological setting, age, sex, and prevalence of clinical disease.

Occasionally, countrywide programmes are launched without pilot evaluations beforehand. In this instance concurrent controls are unavailable. Comparisons must be made between conditions prevailing before and after the institution of the programme (*historical* controls). Such comparisons are far less definitive. Variations in harvests, epidemic diseases (gastroenteritis, measles, etc.), and the like can all influence the incidence and prevalence of xerophthalmia independent of the intervention programme itself. Nevertheless, where it is the only available basis for evaluation, it should be utilized.

Adequate baseline data must be accumulated before initiating the intervention programme, especially when utilizing historical controls.

As a rough rule of thumb, 40 cases are required in the control group to have a reasonable chance of demonstrating effectiveness in a programme that reduces the rate of disease by at least 50 %. Less successful programmes require correspondingly larger numbers of control cases to be proven effective. Sufficient numbers of control cases should be chosen to demonstrate effectiveness at the lowest level considered to justifiy continuing the programme.

In addition to absolute levels of effectiveness, evaluation of the efficiency, strengths, and weaknesses of a programme may indicate how it could be improved.

Appendix 1

EXAMINING EYES AND HANDLING BLOOD SAMPLES IN THE FIELD

Examining eyes

Examining large numbers of children under field survey conditions can present a real challenge to the clinician who is more used to hospital or clinical practice. The following points should be kept in mind.

1. The children are often quite frightened and expect "the worst" (a "needle" or vaccination). The ophthalmologist should be reassuring and adopt a non-threatening attitude.

2. Especially frightened or troublesome children should be examined last. Their cries and struggles will only upset the others.

3. The child is often reassured if held or accompanied by a parent. The ophthalmologist should keep his hands at his side or behind his back, and get as good a view as possible before disturbing the child. He may then advance his hands slowly, preferably from behind the child's head. If the child begins to squirm, the parent can be instructed to separate the lids gently. These procedures are usually effective and preclude the need for a physical struggle.

4. Above all, the ophthalmologist's primary responsibility is to get an adequate view of the entire globe. Where the child is intractable to gentler techniques, he may be laid upon a parent's or an assistant's lap, his arms and legs held firmly and his head stabilized between the legs of the examiner. It is then usually possible to prise the lids apart with the thumb and forefinger of one hand, leaving the other hand free to direct the handlight. In those rare instances in which the lids cannot be

separated with the fingers, a Desmarres or bent paperclip "lid retractor" may be employed by the ophthalmologist.

5. The best, least threatening means of illuminating the globe is with natural lighting. The examiner should be seated in *open shade* (beside a building, under a tree, etc.) with his back to a sunlit area. The child should face the sunlit area without looking directly into the sun itself. After examination of the globe, a handlight may be slowly advanced to the side of the eye to reveal the fine irregularities of corneal and conjunctival xerosis with greater clarity.

6. The ophthalmologist's hands and lid retractors must be kept clean and, in the case of the latter, sterile. This is easily accomplished by soaking them in alcohol and then rinsing them in sterile water.

Collecting and handling blood samples

Blood should be collected away from the general examining area, so as not to scare off the other children. The child is held still by a parent or assistant, the finger (or the heel in the case of an infant) is wiped clean with an alcohol swab and pierced with a sterile lancet, and a total of 0.3–0.4 ml of blood is collected in capillary tubes. The tubes may be conveniently sealed by heating one end in the flame of a candle for 2–3 seconds and then pushing the heated end into the molten wax at the base of the flame. All capillary tube samples from a single individual are placed, sealed end down, in a test-tube which is then capped and labelled. The test-tube should be placed in a plastic container immersed in a vacuum flask containing ice. Thus preserved in a dark, cool place, the samples can wait until the end of the day to be spun in a centrifuge until the plasma is clear, scored, snapped above the level of the packed cells, and the tubes containing the remaining serum then resealed with molten wax. The serum should remain in a cold vacuum flask or refrigerator until it is processed (preferably within 1–2 weeks). Frozen samples can probably be stored somewhat longer, but should be thawed only once, just before processing. Extensively haemolysed samples should be discarded.

When retinol (vitamin A) determinations are performed locally, occasional split samples should be forwarded to a reference laboratory to ensure standardization.

Appendix 2

XEROPHTHALMIA FIELD SURVEY FORMS

General Comments

The following field survey forms are modifications of those found useful in the Indonesian Nutritional Blindness Prevention Project. They are examples of the *types* of information and format that can be employed, but should be modified depending upon local conditions, interests, and abilities. They have been kept simple and include only those factors felt to be most relevant to an understanding of the xerophthalmia problem.

Clinical examination form

This form is primarily intended for children under the age of 6. If older individuals are to be examined or other major causes of blindness exist or are of interest (e.g., trachoma, onchocerciasis, etc.), it should be modified and expanded. A full-scale paediatric or nutritional survey would include many additional measurements.

The ocular examination must be carried out by someone familiar with the clinical manifestations of xerophthalmia, preferably an ophthalmologist. The location and size of all corneal abnormalities should be carefully indicated in the circles provided.

The summation coding format maintains discrete information while economizing on punch-card columns. Simply circle the score for each abnormality present, add the scores for each section, and transfer the totals to the appropriate columns alongside. Where none of the abnormalities listed is present, the total is "0"; this should be entered in the appropriate space. At the completion of the examination, there should be a digit in each of the numbered spaces, even if it is "0".

Clinical Examination Form

Date _____ Enumerator _____

Team _____ Ophthalmologist _____

Sample site _____

Head of family. Name _____ Family number (1) (2) (3)

Individual. Name _____ Number (4) (5) (6)

(7) (8)

* Sex:1 = male 2 = female (9)

* Age: date of birth _____ month _____ year

** Age in months completed (99 = unknown) (10) (11)

Age in years completed (often estimated) (12) (13)

Examination completed: 0 = yes 1 = no (14)

* Include only if not already part of a census/socioeconomic form.
** Collect only for those 6 years and under.

Estimate of potential visual acuity	OD	OS	OD	OS
Clarity of cornea less than 6/60	1	1		
Clarity of lens less than 6/60	2	2		
Total			(15)	(16)
Lids	OD	OS	OD	OS
Entropion	1	1		
Trichiasis	2	2		
Inflamed	4	4		
Total			(17)	(18)
Chalazion	1	1		
Inflamed chalazion	2	2		
Total			(19)	(20)
Conjunctiva				
Injection	1	1		
Phlyctenule	2	2		
Total			(21)	(22)
Non-purulent discharge	1	1		
Purulent discharge	2	2		
Total			(23)	(24)
Xerosis: temporal	1	1		
nasal	2	2		
other	4	4		
Total			(25)	(26)
"Foam" or "cheese": temporal	1	1		
nasal	2	2		
other	4	4		
Total			(27)	(28)
Cornea	OD	OS	OD	OS
Xerosis	1	1		
Erosion	2	2		
Ulcer	4	4		
Total			(29)	(30)

Indicate location of abnormalities

 = xerosis

 = erosion

 = ulcer

		OD	OS		
Keratomalacia:	clear	1	1		
	opaque	2	2		
	perforation	4	4		
	Total			(31)	(32)

Indicate location of keratomalacia:

 = keratomalacia

 = keratomalacia with perforation

		OD	OS		
Corneal scar:	macula/nebula	1	1		
	leucoma	2	2		
	adherent leucoma	4	4		
	Total			(33)	(34)

Indicate location of scar:

 = macula/nebula

 = leucoma

 = adherent leucoma

		OD	OS		
Corneal destruction:	staphyloma	1	1	OD	OS
	phthisis bulbi	2	2		
	descemetocele	4	4		
	Total			(35)	(36)

Historical data on corneal scars and destruction

Historian: 0 = reliable 1 = possibly reliable
2 = unreliable or unavailable

(37)

Age at which lesion occurred:

0 = less than 1 month of age
1 = 1–6 months of age
2 = 7–12 months of age
3 = 1 year completed
4 = 2 years completed
5 = 3 years completed
6 = 4 years completed
7 = 5–6 years completed
8 = over 6 years completed
9 = unknown

(38) (39)

Other events 4 weeks or less before lesion occurred:

Eye trauma	1	1
Measles	2	2
Purulent infection	4	4
Total		

(40) (41)

Marked diarrhoea	1	1
Marked malnutrition	2	2
Marked cough	4	4
Total		

(42) (43)

Was medicine applied to the eye before corneal lesion appeared?

0 = no 1 = yes

(44) (45)

Diagnosis based on clinical examination and history:

1 = trauma
2 = measles
3 = purulent eye infection
4 = congenital
5 = keratomalacia
6 = other
7 = uncertain

(46) (47)

Additional data

Classification

1 = random subsample
2 = abnormal
3 = age/sex/local matched control

(48)

Height (to nearest 0.5 cm) (49) (50) (51) . (52)

Weight (to nearest 0.1 kg) (53) (54) . (55)

Blood obtained 0 = yes 1 = no (56)

Serum vitamin A level (57) (58)

Dietary history form

A "qualitative" individual dietary history form is presented. A family-based form would be quite similar: enquire about foods prepared for the family (as opposed to merely those consumed by the child) and omit questions about breast-feeding.

Major categories of food, but only a few specific items, are indicated. The final choice of food items to be listed depends upon local circumstances. For example, wheat is a potentially important vehicle for vitamin A fortification in Indonesia: none is grown locally and all imported wheat is processed in three factories. An extensive list of wheat-based foodstuffs was therefore included in the Indonesian study. This would not be appropriate, however, where wheat is widely grown and processed at a myriad of village mills.

A quantitative (24-hour recall) dietary history follows the same format as the qualitative forms, but it is the total amount of each food item consumed by the child during the past 24 hours (coded in appropriately graduated amounts), rather than the frequency, that is investigated.

As in the case of the clinical examination form, a full-scale nutritional survey would require more detailed information covering a more extensive list of items.

Qualitative Dietary History Form

Sample site _____ (1) (2) (3)

Head of family. Name _____ Family number (4) (5) (6)

Individual. Name _____ Number (7) (8)

Classification: abnormal 1
control 2
random subsample 4
Total ___ (9)

Items consumed by the child during the past two months

Left-hand column: The frequency with which items were consumed:
1 = several times a day, nearly every day
2 = once a day, nearly every day
3 = less than every day, but at least once a week
4 = less than once a week, but at least once a month
5 = less than once a month
0 = never

Right-hand column: Source of items consumed:
1 = harvested by the family
2 = bought
3 = harvested and bought
0 = inapplicable (item not consumed)

Staples	*Frequency*	*Source*
Rice		
Cassava	___	___
etc.	___	___

Sources of retinol	*Frequency*	*Source*
Liver		
Meat	___	___
Eggs	___	___
Fish	___	___
Fish liver oil	___	___
etc.	___	___

Sources of β-carotenes		
Amaranth		
Cassava leaves	___	___
Drumstick leaves	___	___
Mango	___	___
Papaya	___	___
etc.	___	___

Potentially fortifiable items		
Salt		
Refined sugar	___	___
Monosodium glutamate	___	___
Cooking oils	___	___
Soy sauce	___	___
Powdered milk	___	___
etc.	___	___

If not consumed, reasons why:

1 = unavailable
2 = too expensive
3 = child doesn't like it
4 = child too young
5 = bad for the child
6 = other

Sources of retinol _____

If considered "bad for the child", reason why:

_____

_____

If " other", explanation: _____

_____

Sources of β-carotene _____

If considered "bad for the child", reason why:

_____

_____

If "other", explanation: _____

_____

Frequency breast-fed per day _____

1 = once
2 = twice
3 = 3 times
4 = 4 times
5 = 5 or more times
0 = never or no longer breast-fed

Age of child when breast-feeding ceased: _____

0 = never breast-fed
1 = less than 1 month
2 = 1–3 months
3 = 3–6 months
4 = 6–12 months
5 = 1–2 years
6 = more than 2 years
9 = not applicable (still breast-fed)

Clinic-based case-reporting form

A simple line listing, as shown here, is sufficiently detailed to monitor the number, types, and origin of cases presenting at treatment facilities. It has been kept short and simple to facilitate its use by overworked clinic personnel.

Xerophthalmia case-reporting form

Clinical facility _____

Case number	Date	Patient's name	Village or locality	Age	Sex	Record all abnormalities present						
						XN	X1B		X2		X3	
							OD	OS	OD	OS	OD	OS
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												

SELECTED BIBLIOGRAPHY

The following publications are useful for gaining further insight into the general problem of xerophthalmia and related conditions, as well as specific aspects that are only touched upon in this manual.

Comprehensive discussions of vitamin A deficiency and xerophthalmia, with extensive lists of references

Vitamin A deficiency and xerophthalmia. Report of a joint WHO/USAID meeting, Geneva, World Health Organization, 1976 (Technical Report Series, No. 590)

McLaren, S. M. *Malnutrition and the eye*, New York, Academic Press, 1963
(A new edition of this classic treatise is in preparation.)

Assessment and intervention

International Vitamin A Consultative Group (IVACG). *Guidelines for the eradication of vitamin A deficiency and xerophthalmia*, New York, The Nutrition Foundation, 1975

Nutritional requirements, surveys, food fortification

bauernfeind, J. C. & Cort, W. M. Nutrification of foods with added vitamin A. *CRC Critical Reviews in Food Technology*, **4**: 337–375 (1974)

Jelliffe, D. B. *The assessment of the nutritional status of the community*, Geneva, World Health Organization, 1966 (Monograph Series, No. 53)

Passmore, R., et al. *Handbook on human nutritional requirements*, Rome, Food and Agriculture Organization of the United Nations, 1974 (FAO Nutritional Studies No. 28)

WHO publications on related fields of blindness prevention

Buck, A. A., ed. *Onchocerciasis. Symptomatology, pathology, diagnosis*, Geneva, World Health Organization, 1974

Tarizzo, M. L., ed. *Field methods for the control of trachoma*, Geneva, World Health Organization, 1973

* * *

Food composition

Food composition tables, each issue covering a different part of the world, are available from the Food and Agriculture Organization of the United Nations, Rome, and the US Department of Health, Education, and Welfare, Public Health Service, Washington, DC.

Xerophthalmia training aides

A variety of training aides are available at nominal cost, from Helen Keller International, 22 West 17th Street, New York, NY, 10011. These range from simple flip charts for instructing village mothers to self-contained lectures and slides for teaching medical students and physicians.

WHO publications may be obtained, direct or through booksellers, from :

ALGERIA	Société Nationale d'Edition et de Diffusion, 3 bd Zirout Youcef, ALGIERS.
ARGENTINA	Carlos Hirsch SRL, Florida 165, Galerías Güemes, Escritorio 453/465, BUENOS AIRES.
AUSTRALIA	*Mail Order Sales :* Australian Government Publishing Service Bookshops, P.O. Box 84, CANBERRA A.C.T. 2600 ; *or over the counter from :* Australian Government Publications and Inquiry Centres at : 113–115 London Circuit, CANBERRA CITY A.C.T. 2600 ; Shop 42, The Valley Centre, BRISBANE, Queensland 4000 ; 347 Swanston Street, MELBOURNE, VIC 3000 ; 309 Pitt Street, SYDNEY, N.S.W. 2000; Mt. Newman House, 200 St. George's Terrace, PERTH, WA 6000; Industry House, 12 Pirie Street, ADELAIDE, SA 5000 ; 156–162 Macquarie Street, HOBART, TAS 7000 — Hunter Publications, 58A Gipps Street, COLLINGWOOD, VIC 3066.
AUSTRIA	Gerold & Co., Graben 31, 1011 VIENNA I.
BANGLADESH	WHO Representative, G.P.O. Box 250, DACCA 5 — The Association of Voluntary Agencies, P.O. Box 5045, DACCA 5.
BELGIUM	Office international de Librairie, 30 avenue Marnix, 1050 BRUSSELS — *Subscriptions to World Health only :* Jean de Lannoy, 112 rue du Trône, 1050 BRUSSELS.
BRAZIL	Biblioteca Regional de Medicina OMS/OPS, Unidade de Venda de Publicações, Caixa Postal 20.381, Vila Clementino, 04023 SÃO PAULO, S.P.
BURMA	*see* India, WHO Regional Office.
CANADA	*Single and bulk copies of individual publications (not subscriptions) :* Canadian Public Health Association, 1335 Carling Avenue, Suite 210, OTTAWA, Ont. K1Z 8N8. *Subscriptions : Subscription orders, accompanied by cheque made out to the* Royal Bank of Canada, Ottawa, Account World Health Organization, *should be sent to the* World Health Organization, P.O. Box 1800, Postal Station B, OTTAWA, Ont. K1P 5R5. *Correspondence concerning subscriptions should be forwarded to the* World Health Organization, Distribution and Sales, 1211 GENEVA 27, Switzerland.
CHINA	China National Publications Import Corporation, P.O. Box 88, PEKING.
COLOMBIA	Distrilibros Ltd, Pío Alfonso García, Carrera 4a, Nos 36–119, CARTAGENA.
CZECHO-SLOVAKIA	Artia, Ve Smeckach 30, 111 27 PRAGUE 1.
DENMARK	Ejnar Munksgaard Ltd, Nørregade 6, 1164 COPENHAGEN K.
ECUADOR	Librería Científica S.A., P.O. Box 362, Luque 223, GUAYAQUIL.
EGYPT	Nabaa El Fikr Bookshop, 55 Saad Zaghloul Street, ALEXANDRIA.
EL SALVADOR	Librería Estudiantil, Edificio Comercial B No 3, Avenida Libertad, SAN SALVADOR.
FIJI	The WHO Representative, P.O. Box 113, SUVA.
FINLAND	Akateeminen Kirjakauppa, Keskuskatu 2, HELSINKI 00101.
FRANCE	Librairie Arnette, 2 rue Casimir-Delavigne, 75006 PARIS.
GERMAN DEMOCRATIC REPUBLIC	Buchhaus Leipzig, Postfach 140, 701 LEIPZIG.
GERMANY, FEDERAL REPUBLIC OF	Govi-Verlag GmbH, Ginnheimerstrasse 20, Postfach 5360, 6236 ESCHBORN — W. E. Saarbach, Postfach 101 610, Follerstrasse 2, 5 COLOGNE 1 — Alex. Horn, Spiegelgasse 9, Postfach 3340, 62 WIESBADEN.
GREECE	G. C. Eleftheroudakis S.A., Librairie internationale, rue Nikis 4, ATHENS (T. 126).
HAITI	Max Bouchereau, Librairie "A la Caravelle", Boîte postale 111-B, PORT-AU-PRINCE.
HONG KONG	Hong Kong Government Information Services, Beaconsfield House, 6th Floor, Queen's Road, Central, VICTORIA.
HUNGARY	Kultura, P.O.B. 149, BUDAPEST 62 — Akadémiai Könyvesbolt, Váci utca 22, BUDAPEST V.
ICELAND	Snaebjørn Jonsson & Co., P.O. Box 1131, Hafnarstraeti 9, REYKJAVIK.
INDIA	WHO Regional Office for South-East Asia, World Health House, Indraprastha Estate, Ring Road, NEW DELHI 110002 — Oxford Book & Stationery Co., Scindia House, NEW DELHI 110000 ; 17 Park Street, CALCUTTA 700016 (Sub-agent).
INDONESIA	M/s Kalman Book Service Ltd, Jln. Cikini Raya No. 63, P.O. Box 3105/Jkt, JAKARTA.
IRAN	Iranian Amalgamated Distribution Agency, 151 Khiaban Soraya, TEHERAN.
IRELAND	The Stationery Office, DUBLIN 4.
ISRAEL	Heiliger & Co., 3 Nathan Strauss Street, JERUSALEM.
ITALY	Edizioni Minerva Medica, Corso Bramante 83–85, 10126 TURIN ; Via Lamarmora 3, 20100 MILAN.
JAPAN	Maruzen Co. Ltd, P.O. Box 5050, TOKYO International 100–31.
KENYA	The Caxton Press Ltd, Gathani House, Homa Bay Road, P.O. Box 41742, NAIROBI.
KUWAIT	The Kuwait Bookshops Co. Ltd, Thunayan Al-Ghanem Bldg, P.O. Box 2942, KUWAIT.
LAO PEOPLE'S DEMOCRATIC REPUBLIC	The WHO Representative, P.O. Box 343, VIENTIANE.
LEBANON	Documenta Scientifica/Redico, P.O. Box 5641, BEIRUT.
LUXEMBOURG	Librairie du Centre, 49 bd Royal, LUXEMBOURG.

A/1/78

WHO publications may be obtained, direct or through booksellers, from:

MALAYSIA	The WHO Representative, Room 1004, Fitzpatrick Building, Jalan Raja Chulan, KUALA LUMPUR 05–02 — Jubilee (Book) Store Ltd, 97 Jalan Tuanku Abdul Rahman, P.O. Box 629, KUALA LUMPUR 01–08 — Parry's Book Center, K. L. Hilton Hotel, Jln. Treacher, P.O. Box 960, KUALA LUMPUR.
MEXICO	La Prensa Médica Mexicana, Ediciones Científicas, Paseo de las Facultades, 26, Apt. Postal 20–413, MEXICO CITY 20, D.F.
MONGOLIA	*see* India, WHO Regional Office.
MOROCCO	Editions La Porte, 281 avenue Mohammed V, RABAT.
MOZAMBIQUE	INLD, Caixa Postal 4030, MAPUTO.
NEPAL	*see* India, WHO Regional Office.
NETHERLANDS	N.V. Martinus Nijhoff's Boekhandel en Uitgevers Maatschappij, Lange Voorhout 9, THE HAGUE 2000.
NEW ZEALAND	Government Printing Office, Mulgrave Street, Private Bag, WELLINGTON 1. *Government Bookshops at :* Rutland Street, P.O. 5344, AUCKLAND ; 130 Oxford Terrace P.O. Box 1721, CHRISTCHURCH ; Alma Street, P.O. Box 857, HAMILTON ; Princes Street, P.O. Box 1104, DUNEDIN — R. Hill & Son Ltd, Ideal House, Cnr Gillies Avenue & Eden Street, Newmarket, AUCKLAND 1.
NIGERIA	University Bookshop Nigeria Ltd, University of Ibadan, IBADAN.
NORWAY	Johan Grundt Tanum Bokhandel, Karl Johansgt. 43, 1010 OSLO 1.
PAKISTAN	Mirza Book Agency, 65 Shahrah Quaid-E. Azam, P.O. Box 729, LAHORE 3.
PHILIPPINES	World Health Organization, Regional Office for the Western Pacific, P.O. Box 2932, MANILA — The Modern Book Company Inc., P.O. Box 632, 926 Rizal Avenue, MANILA.
POLAND	Składnica Księgarska, ul Mazowiecka 9, 00052 WARSAW *(except periodicals)* — BKWZ Ruch, ul Wronia 23, 00840 WARSAW *(periodicals only)*.
PORTUGAL	Livraria Rodrigues, 186 Rua do Ouro, LISBON 2.
REPUBLIC OF KOREA	The WHO Representative, Central P.O. Box 540, SEOUL.
SINGAPORE	The WHO Representative, 144 Moulmein Road, G.P.O. Box 3457, SINGAPORE 11 — Select Books (Pte) Ltd, 215 Tanglin Shopping Centre, 2/F, 19 Tanglin Road, SINGAPORE 10.
SOUTH AFRICA	Van Schaik's Bookstore (Pty) Ltd, P.O. Box 724, PRETORIA 0001.
SPAIN	Comercial Atheneum S.A., Consejo de Ciento 130–136, BARCELONA 15 ; General Moscardó 29, MADRID 20 — Librería Díaz de Santos, Lagasca 95, MADRID 6 ; Balmes 417 y 419, BARCELONA 6.
SRI LANKA	*see* India, WHO Regional Office.
SWEDEN	Aktiebolaget C. E. Fritzes Kungl. Hovbokhandel, Regeringsgatan 12, 10327 STOCKHOLM.
SWITZERLAND	Medizinischer Verlag Hans Huber, Länggass Strasse 76, 3012 BERNE 9.
THAILAND	*see* India, WHO Regional Office.
TUNISIA	Société Tunisienne de Diffusion, 5 avenue de Carthage, TUNIS.
TURKEY	Librairie Hachette, 469 avenue de l'Indépendance, ISTANBUL.
UNITED KINGDOM	H.M. Stationery Office : 49 High Holborn, LONDON WC1V 6HB ; 13a Castle Street, EDINBURGH EH2 3AR ; 41 The Hayes, CARDIFF CF1 1JW ; 80 Chichester Street, BELFAST BT1 4JY ; Brazennose Street, MANCHESTER M60 8AS ; 258 Broad Street, BIRMINGHAM B1 2HE ; Southey House, Wine Street, BRISTOL BS1 2BQ. *All mail orders should be sent to* P.O. Box 569, LONDON SE1 9NH.
UNITED STATES OF AMERICA	*Single and bulk copies of individual publications (not subscriptions) :* WHO Publications Centre USA, 49 Sheridan Avenue, ALBANY, N.Y. 12210. *Subscriptions : Subscription orders, accompanied by check made out to the* Chemical Bank, New York, Account World Health Organization, *should be sent to the* World Health Organization, P.O. Box 5284, Church Street Station, NEW YORK, N.Y. 10249 ; *Correspondence concerning subscriptions should be forwarded to the* World Health Organization, Distribution and Sales, 1211 GENEVA 27, Switzerland. *Publications are also available from the* United Nations Bookshop, NEW YORK, N.Y. 10017 *(retail only)*.
USSR	*For readers in the USSR requiring Russian editions :* Komsomolskij prospekt 18, Medicinskaja Kniga, MOSCOW — *For readers outside the USSR requiring Russian editions :* Kuzneckij most 18, Meždunarodnaja Kniga, MOSCOW G-200.
VENEZUELA	Editorial Interamericana de Venezuela C.A., Apartado 50785, CARACAS 105 — Librería del Este, Apartado 60337, CARACAS 106.
YUGOSLAVIA	Jugoslovenska Knjiga, Terazije 27/II, 11000 BELGRADE.

Special terms for developing countries are obtainable on application to the WHO Representatives or WHO Regional Offices listed above or to the World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland. Orders from countries where sales agents have not yet been appointed may also be sent to the Geneva address, but must be paid for in pounds sterling, US dollars or Swiss francs.

Price: Fr. s. 10.–

Prices are subject to change without notice.